ASID: A Bayesian Adaptive Subgroup-Identification Enrichment Design

by

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Abstract

It has been observed and is generally accepted that patients with a given disease may respond differently to the same treatment. Hence, it is sensible to believe that there are subgroups of patients, delineated by their biomarker profiles, wherein certain treatments are better choices than others. However, it is difficult to predict a priori which patients are good candidates for a given treatment; an ideally designed trial would adaptively find and update subgroups of patients at an interim analysis point. We propose a method that does exactly this: ASID, for Adaptive Subgroup-Identification and enrichment Design. ASID finds predictive biomarkers, estimates which patient subgroups have differential treatment effects, and modifies the trial recruitment criteria at an interim analysis point. Moreover, ASID is based on a hierarchical Bayesian model. In this work, motivated by an Alzheimer's Disease clinical trial, we derive and analyze ASID, and compare it to an alternative adaptive enrichment design built around a linear regression model as well as to a random forest based model (GUIDE). Via numerical simulations, we demonstrate the superiority of ASID.

Advisor: Dr. Yanxun Xu

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1 Introduction

This thesis is concerned with clinical trial design, that is, statistically designed experiments for evaluating the efficacy of new (medical) drugs. In particular, this work is about an adaptive, Bayesian method for clinical trial design. In this introductory section, we discuss the basics of Bayesian reasoning and clinical trial design, as well as why it is sensible to marry the two. We then follow our review of Bayesian principles with a discussion of adaptive designs and subgroup identification.

1.1 Bayesian Methods

The broadly stated goal of Bayesian inference is to find a posterior distribution for parameters of interest given data and a particular model. A good overview is Hoff (2009). The main vehicle toward the goal of obtaining a posterior distribution is Bayes' Theorem.

1.1.1 Bayes' Theorem

Bayes' theorem is one of the most fundamental laws in probability. It originates in a posthumously published work by the reverend Thomas Bayes (Bayes, 1763). The original work was specific to a special case of what we now call the Binomial distribution, and in 1774, Laplace generalized the theorem and stated it in the modern form seen today (de Laplace, 1774).

The statement of Bayes' theorem is as follows. Assume that we have events A and B, where B has a non-zero probability $p(B)$. Then we have that

$$p(A \mid B) = \frac{p(B \mid A) \times p(A)}{p(B)},$$

where $p(A \mid B)$ is the conditional probability of A given B.

The utility of this theorem will be apparent throughout this thesis, especially in the following way. Assume that we have a model Π with parameters θ and some data

$Y_n = \{y_1, \cdots, y_n\}$. We have some prior knowledge and beliefs about the parameters θ given our model Π: we capture this in a prior distribution $p(\theta|\Pi)$. Additionally, we define the likelihood $p(Y_n \mid \theta, \Pi)$ and probability of the evidence $p(Y_n \mid \Pi)$. If the posterior distribution of theta is expressed as $p(\theta \mid Y_n, \Pi)$, Bayes' Theorem gives us that

$$\text{Posterior} = \frac{\text{Likelihood} \times \text{Prior}}{\text{Evidence}},$$

or

$$p(\theta \mid Y_n, \Pi) = \frac{p(Y_n \mid \theta, \Pi) \times p(\theta \mid \Pi)}{p(Y_n \mid \Pi)}.$$

Omitting the dependence on the evidence, we may say that

$$\text{Posterior} \propto \text{Likelihood} \times \text{Prior},$$

or that

$$p(\theta \mid Y_n, \Pi) \propto p(Y_n \mid \theta, \Pi) \times p(\theta \mid \Pi).$$

1.1.2 Bayesian Clinical Trial Design

A general overview of the use of Bayesian methods in medicine is found in Ashby (2006) and the textbooks Berry et al. (2010) and Spiegelhalter et al. (2004). A theme until recently was that Bayesian methods were interesting, but never practical because of their greater computational needs. Hence, while there have been proponents such as Cornfield (1969) since the 1960s, it was not until recently that meaningful leaps to implement Bayesian methods were made.

A proponent of Bayesian methods in clinical trial design, Donald Berry, provides an overview of the advantages of a Bayesian design relative to a frequentist approach (Berry, 2006). In particular, an earlier work from 2002 suggests that the main avenue of frequentist criticisms, prior misspecification, is not a serious concern, in the sense that the error from a misspecified prior is quantifiably small (Berry et al., 2002). Additionally, some of the advantages pointed out in Spiegelhalter et al. (2004) include the greater influence of evidence on the reasoning process, explicit modeling of biases,

and the hierarchical model framework that allows 'pooling of evidence' from multiple sources.

However, there are concerns that are yet unaddressed: between phases of a clinical trial, whether it is sensible to use prior information, and whether 'adversarial' priors could be chosen by researchers to bias the results toward a company's financial gain (Howard et al., 2005). Additionally, Bayesian techniques are unfamiliar and new to many practitioners, so there are no established standards and thus there is a danger of misuse stemming from unfamiliarity.

Despite the relative novelty of Bayesian methods in clinical trials, there have been increasingly many papers and studies based around them. For example, the work in Thall and Simon (1994) proposed a Bayesian phase II clinical trial design with a binary outcome. The trial has two stopping conditions: when the treatment under investigation has a high posterior probability of being promising or not being promising, or when the maximum sample size is reached. One of the strengths of this approach is being able to terminate an inconclusive or unfruitful trial early.

Another interesting work is Simon (1999). This study compares an 'experimental treatment' to a control, and derives the posterior probability that the experimental treatment is superior to a placebo and the control (with varying degrees of superiority), and that the control is superior to the placebo. The idea behind this approach is that the frequentist method of conducting a hypothesis test with some cutoff is arbitrary, since the choice of cutoff is itself arbitrary in the absence of knowledge of how much more effective than the placebo the control treatment is. Instead, quantifying the evidence for the effectiveness of each treatment is a more quantitative approach.

Finally, a well-known, real clinical trial is the I-SPY 2 breast cancer trial (Barker et al., 2009). This trial effectively made use of biomarker data, and compared two groups given a standard chemotherapy treatment (control) with five groups given different, new drugs in addition to the chemotherapy. The design of the trial was adaptive, and formed assignments based on the biomarker profiles and drug success relative to biomarker profiles. Additionally, drugs with universally low posterior probabilities of success were dropped, while those with a high posterior probability

of being more successful than the control would 'graduate' to a phase III trial.

1.1.3 Markov Chain Monte Carlo

Markov Chain Monte Carlo (MCMC) methods are a class of numerical methods for sampling from otherwise intractable distributions. For example, we may know the shape of a distribution but not the normalizing constant. Or, we may know the density function, but the function is complicated and there is no easy way to form the distribution function and/or invert it. This class of methods was introduced by Hastings in 1970 (Hastings, 1970). An important development came in 1984 with Gibbs sampling (Geman and Geman, 1984).

MCMC methods are essential for practical Bayesian inference. Often, we do not know the normalizing constant of a posterior distribution, and even more often, we cannot sample from a posterior distribution directly, to say nothing of computing statistics of interest like the posterior mean or median. The development of faster and better computers from the 1990s onward and some mainstream practical implementations of MCMC methods in recent years have contributed to the acceleration of practical Bayesian inference.

We conclude this discussion of MCMC techniques with an overview of the algorithm we use in our numerical simulations: the Metropolis-Hastings sampler (Robert and Casella, 2013). Formally, the goal is to sample from a distribution with probability density $p(x)$. However, we only have knowledge of $f(x)$, where $f(x)$ is proportional to $p(x)$. Assume that we desire M total samples, and have chosen a proposal distribution with density g. Assume further that we discard the first B samples (burn-in) to ensure convergence to the stationary distribution and thereafter only keep every T^{th} sample to ensure that the samples are decorrelated. Then, the algorithm is as follows:

MH.1 Choose an initial state x randomly within the support of $f(x)$ (which is the same as that of $p(x)$).

MH.2 Sample a new state x' from a proposal distribution with density $g(x' \mid x)$.

The density g can be thought of as the probability of moving to a state x' conditioned on the previous state being x.

MH.3 Form the acceptance distribution

$$A(x' \mid x) \propto f(x') \times g(x \mid x')$$

and

$$A(x \mid x') \propto f(x) \times g(x' \mid x)$$

and then the acceptance ratio

$$\alpha(x, x') = \frac{A(x' \mid x)}{A(x \mid x')} = \frac{f(x') \times g(x \mid x')}{f(x) \times g(x' \mid x)}.$$

MH.4 Accept and store the state x' with probability $\min\{\alpha(x, x'), 1\}$.

MH.5 When $B + TM$ states have been accepted and stored, proceed to Step **MH.6**. Otherwise return to Step **MH.2**.

MH.6 Discard the first B stored states, and then discard all but every T^{th} state so that there are M states (samples) returned.

Details on the exact implementation of this algorithm for the work found in this thesis are given in Appendix G.

1.2 Subgroup Identification

Often, the same treatment will react differently in two patients with the same disease. That is, the response to a treatment varies across some latent subgroups of patients, where these subgroups are characterized by the patients' physiological characteristics: biomarkers. If the same treatment can lead to significantly different responses in two patients with the same disease, a clinical trial should in addition to evaluating the efficacy of the treatment, characterize for which patients it is effective. Simply put, a clinical trial should also identity the patient subgroups wherein a treatment

is effective. Equivalently, a trial should find which biomarkers and which values of those biomarkers are predictive of treatment success.

An example of how and why subgroup identification is important is found in a recent study of breast cancer patients (Hudis, 2007). It was found that the medication trastuzumab is only a good choice for patients with an 'enriched HER2 pathway'. In this study, the conclusion was that matching certain genetic traits (biomarkers) to various treatments was optimal. A second example of subgroup identification is found in a study of patients with colorectal cancer (Misale et al., 2012). In particular, the study found that patients with KRAS mutated colorectal cancer should not be given treatment with EGFR antibodies. These real examples showcase the importance of subgroup identification.

A flagship frequentist method that we will compare our methods against is GUIDE (Loh et al., 2015). GUIDE is a regression tree-based method, wherein variable selection via χ^2-tests identifies which variables to split on, and the splits yield the subgroups which have differential treatment effects. The work in Shen and He (2015) is related, and used a structured logistic-normal mixture model to form tests to confirm the existence of subgroups. These methods are not specific to clinical trials, and indeed have not been applied directly in this setting: they are general subgroup identification methods.

Perhaps the most immediate starting points for this work are SUBA (Xu et al., 2014) and its extension SCUBA (Guo et al., 2016). SUBA is a Bayesian Subgroup-Based Adaptive design wherein a random partition model (akin to a tree) partitions the patient biomarker space by splitting along the median of the observed values. The goal of the partitions is to find an allocation of patients to their optimal treatment. However, the median is often suboptimal and is a priori an arbitrary choice. The work in SCUBA allows for general affine hyperplanes to serve as split boundaries. However, both works are non-adaptive in the sense that the entry criteria is not modified.

1.3 Enrichment Design

As explained in the previous section, it is important for a clinical trial to identify fruitful subgroups for a treatment. However, clinicians may not be aware of the treatment's precise mechanism or even the disease's biochemical characteristics in great detail. Hence, if a clinical trial could *adaptively* change how it recruits patients to more efficiently find the ideal patient biomarker ranges for the treatment under investigation, the chances of success would increase. Methods to do precisely this, modification of the entry criteria at the interim analysis stage, have been developed. Authors in the field term patients with the desired, positive treatment response as "enriched". A recent survey of adaptive designs in real clinical trials is given in Hatfield et al. (2016). The paper is a meta-analysis of recent trials, and showed that the use of adaptive designs is increasing, especially in oncology.

Some prior work in the area is Wang et al. (2007) and Karuri and Simon (2012). Both works are adaptive in the sense that they began with subgroups defined in terms of biomarkers, and at the interim analysis, halted enrollment of patients from the less successful (biomarker negative) subgroups. Additionally, Rosenblum and van der Laan (2011) described an adaptive trial design wherein pre-planned, pre-designed criteria were used to alter entry criteria. The work in Simon and Simon (2013) furthered a series of adaptive updates to the eligibility criteria. The strength of this work lies in the control of the type-I error. The paper Wang and Hung (2013) contains a more detailed survey of adaptive enrichment designs.

The body of work we have just described is not truly adaptive, in the sense that it uses pre-drawn subgroups. This approach may lead to poor outcomes if the subgroups are poorly chosen and are not correlated with treatment outcomes or treatment assignments. Hence, a high quality, truly adaptive enrichment design should include methods for subgroup identification. For example, the work in Sivaganesan et al. (2011) uses a model selection procedure (variable selection on the biomarkers) to find subgroups, and the work in Foster et al. (2011) uses a random forest algorithm to to find regions of the biomarker space where the treatment has a larger-than-average

effect relative to the whole space. Another approach is SIDES, (Lipkovich et al., 2011). SIDES (subgroup identification based on differential effect search), uses a Classification and Regression Tree (CART) (Breiman et al., 1984) to find bisections of the biomarker space wherein the halves have maximally different effect sizes. A very recent work is Trippa et al. (2012), where Bayesian methods for enrichment are studied in the context of a renal cell carcinoma oncology trial. A Bayesian decision-theoretic perspective is used to parametrize a random discontinuation design wherein the results from a first stage are used to identify a subpopulation to enrich.

1.4 A Biomarker-Driven and Subgroup-Based Enrichment Design

This thesis contains a proposed class of adaptive subgroup-identification enrichment designs (ASID). The design uses patient biomarker profiles and patient treatment outcomes as they are found. The ASID algorithm adaptively finds subgroups in the space of biomarkers instead of predefining them. The design allows the clinical entry criteria to be updated in the course of the trial, so that patients who are more likely to respond to the treatment are selected. This choice improves the prospects for finding a clinically significant treatment effect. Additionally, our design is built around a hierarchical Bayesian model: our model is extremely flexible and can handle biomarkers (covariates) of different domains (continuous, binary, categorical, ordinal) and responses (outcomes) of different forms (binary, categorical, continuous, regression).

The ASID algorithm is a novel approach to clinical trial design. It pushes the envelope by its ability to continuously identify and update subgroups of patients with differential treatment effects. Additionally, it is a Bayesian approach. Our approach is superior to preexisting takes on this problem: we only need data from one trial, and we can handle low sample sizes since we adaptively recruit patients in a manner that optimizes the chances of finding a differential treatment effect. Moreover, our approach is far more flexible as a consequence of being adaptive.

1.5 Motivating Trial

The work in this thesis is motivated by a study for a new compound for treating patients with Alzheimer's disease (AD). The study is a double-blind, proof-of-concept (POC) trial, with a placebo as control. The quantitative goal of the study is to effect a beneficial change in patients with AD from their initial baseline measurements, as measured by the 13-point AD Assessment Scale–Cognitive Subscale (ADAS-cog) score.

Prior work in the area (for example, Cummings et al. (2012)) suggests that there are several physiological quantities (biomarkers) that may be good predictors of treatment efficacy. Among other quantities, these biomarkers include apolipoprotein E (APOE)-$\epsilon 4$ genotype and allele status, plasma amyloid precursor protein β (Aβ), and cerebrospinal fluid (CSF) β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1). However, it is possible that the compound under investigation is only effective for certain ranges of one or more biomarkers. That is, there may be subgroups of the population wherein the investigational compound is effective (in a clinically meaningful sense), and outside of which it is less effective (if effective at all). Hence, the goal herein is to marry the tasks of identifying fruitful patient subgroups and population enrichment with the goal of rapid development and investigation of this new compound.

This study proceeds as follows. Patients diagnosed with AD who meet certain clinically given entry criteria will be selected and equally randomized to the placebo or investigational compound. Biomarker data (baseline) will be collected at the start, and at the pre-determined point of the interim analysis, the ADAS-cog scores will be used to find potential subgroups of patients wherein there is a differential treatment effect. If and when such a subgroup is found, the entry criteria will be altered to only accept new patients whose biomarker data places them within the subgroup. In this way, the study allows for population enrichment within the trial, so that more high quality information can be obtained and used to accelerate the next stages of drug development.

1.6 Outline

This thesis is organized as follows. We describe the Bayesian probability models in Section 2. In Section 3, the proposed design (characterized above) is summarized. In the next section, Section 4, we present comprehensive simulation studies and statistical properties of the ASID design. We conclude with Section 5. We defer many technical details and tables of numerical results to the appendices.

2 Probability Model

In this section, we begin by discussing the sampling model, and then follow up with the construction of partitions of the biomarker space to find the patient subgroups.

2.1 Notation

We first define some notation. There are at most N patients, labeled by $i \in \{1, \ldots, N\}$, T treatments labeled by $t \in \{1, \ldots, T\}$ (the motivating AD trial uses $T = 2$), and K biomarkers labeled by $k \in \{1, \ldots, K\}$. Let z_i be the treatment label for patient i. Let $\boldsymbol{x}_i = (x_{i1}, \ldots, x_{iK})'$ denote the biomarker profile for patient i, where x_{ik} is the value of biomarker k for patient i. The biomarkers may be continuous, ordinal, binary, or categorical. The response for patient i is denoted by y_i. We will explicate our model based upon the domain of y_i.

Let Ω be the biomarker space, and let the variable Π denote a partition. A partition is a family of mutually disjoint subsets of Ω whose union is Ω: $\Pi = \{S_1, \ldots, S_M\}$. Let M be the number of subsets in Π, where M is a random variable. Given a partition of the biomarker space, we naturally induce one on the collection of patients. The relationship is the following: if $\boldsymbol{x}_i \in S_m$, we say that patient i belongs to the subgroup with label m.

2.2 Sampling Model

Consider now the sampling model. We divide our explanation into the various cases for the support of y_i.

2.2.1 Binary Outcomes

Binary outcomes are perhaps the simplest, most intuitive sort of outcome: a treatment is successful or it is not. Let $y_i \in \{0, 1\}$ and let $\theta_{t,m}$ denote the response rate of patients

in subgroup m with treatment t. That is, we assume that

$$p(y_i = 1 \mid \boldsymbol{x}_i \in S_m, z_i = t, \Pi) = \theta_{t,m}.$$

Here, the likelihood function is the product of n Bernoulli probability mass functions. The conjugate prior on $\theta_{t,m}|\Pi$ is a Beta distribution. We use the notation $Beta(a, b)$, where this denotes a Beta distribution with mean $a/(a+b)$. The details are found in Appendix C.

2.2.2 Categorical Outcomes

Categorical outcomes extend the binary case to more gradations. Note that binary outcomes are a special case of categorical outcomes with $C = 2$. Indeed, the two types have very similar specifications. Let $y_i \in \{1, 2, \ldots, C\}$, where C is a finite, positive integer. Let $\theta_{c,t,m}$ denote the response rate of patients in subgroup m with treatment t and response c. That is, assume that

$$p(y_i = c \mid \boldsymbol{x}_i \in S_m, z_i = t, \Pi) = \theta_{c,t,m},$$

and that the likelihood is a product of categorical distribution probability mass functions. Moreover, we constrain the $\theta_{c,t,m}$ so that $\sum_{c=1}^{C} \theta_{c,t,m} = 1$. The conjugate prior on $(\theta_{c,t,m})_{c=1}^{C} \mid \Pi$ is a Dirichlet distribution with parameters $(a_c)_{c=1}^{C}$. The details are found in Appendix D.

2.2.3 Continuous Outcomes

For continuous outcomes, let $y_i \in \mathbb{R}$ and let $\theta_{t,m}$ be the average (arithmetic mean) of the patient responses in subgroup m with treatment t. Assume that the responses are conditionally normal, or that

$$p(y_i \mid \boldsymbol{x}_i \in S_m, z_i = t, \Pi) = \mathcal{N}(\theta_{t,m}, \sigma^2),$$

where the notation $\mathcal{N}(a, b)$ denotes the probability density function for a Gaussian random variable with mean a and variance b. It follows that the likelihood can be written as:

$$\prod_{t=1}^{T}\prod_{m=1}^{M}\prod_{\{i:z_i=t,\boldsymbol{x}_i\in S_m\}}(2\pi\,\sigma^2)^{-1/2}\exp\{-\frac{1}{2\sigma^2}(y_i-\theta_{t,m})^2\}. \tag{2.1}$$

The conjugate prior for $\theta_{t,m}$ and σ^2 is the product $p(\theta_{t,m}, \sigma^2) = p(\theta_{t,m}|\sigma^2)p(\sigma^2)$, with $p(\theta_{t,m}|\sigma^2) = \mathcal{N}(\theta_0, \frac{\sigma^2}{\kappa_0})$ and $p(\sigma^2) = IG(\frac{\nu_0}{2}, \frac{SS_0^2}{2})$. In the previous expression, $SS_0^2 = \nu_0\sigma_0^2$ and $IG(a, b)$ denotes the density function for an Inverse Gamma distributed random variable with shape parameter a and rate parameter b. Here, θ_0, κ_0, ν_0, and σ_0^2 are hyperparameters. The details are found in Appendix E.

2.2.4 Linear Regression Model

Consider a variant of continuous outcomes, wherein y_i is a linear transformation of the biomarker vector $\boldsymbol{x}_i$: $y_i = \boldsymbol{x}_i'\boldsymbol{\beta}_{t,m} + \epsilon_i$, where $\boldsymbol{\beta}_{t,m}$ is the linear regression coefficient vector for patients in subgroup m with treatment t. We let $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$, where $\mathcal{N}(a, b)$ denotes the Gaussian distribution with mean a and variance b. We use conjugate priors on $\boldsymbol{\beta}_{t,m}$ and σ^2: $\boldsymbol{\beta}_{t,m} \sim \mathcal{N}(\mu_0, \Sigma_0)$ and $\sigma^2 \sim IG(a_0, b_0)$. Under this setup, the posterior distributions of $\boldsymbol{\beta}_{t,m}$ and σ^2 are multivariate normal and inverse Gamma distributions, respectively. The details are found in Appendix F.

2.2.5 Joint Model

Let Θ denote the parameters in the sampling model. Furthermore, let $\boldsymbol{Y}_n = (y_1, \ldots, y_n)$, $\boldsymbol{X}_n = (x_1, \ldots, x_n)$, and $\boldsymbol{Z}_n = (z_1, \ldots, z_n)$. We can now package the sampling models and priors in one expression:

$$p(\boldsymbol{Y}_n, \Theta, \Pi \mid \boldsymbol{X}_n, \boldsymbol{Z}_n) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \Pi)\, p(\Theta \mid \Pi)\, p(\Pi \mid \boldsymbol{c})p(\boldsymbol{c}), \tag{2.2}$$

where we use $\boldsymbol{c}$ to represent the model parameters describing the partition Π. The details for each expression depend on the response type, and can be found in the

immediately preceding sections.

2.3 The Partition Π

In this section, we describe the construction of the partition Π. Here, we will focus on the intuition and give a general characterization. In Appendix A, we present a detailed examination of the construction. Additionally, in Appendix B, we present a brief combinatorial characterization of the partitions.

We begin with the biomarker space Ω, and choose a biomarker k and a threshold τ_k for the first split. The choice of a threshold τ_k bisects Ω into two disjoint subsets: the first subset contains all points in Ω with biomarker k (coordinate k) smaller than or equal to τ_k, and the second subset contains all other points. In the case that biomarker k takes categorical values (discrete with no ordering), τ_k is a subset of values, and we have one subset given by points in Ω with biomarker k valued in τ_k and the other by those points with biomarker k not in τ_k.

After the first split, we have two subsets. For the second split, we bisect each of the subsets in a similar manner to the first split. That is, within the first subset, we split along a threshold τ_{k_1} in biomarker k_1, and within the second, we split along τ_{k_2} in biomarker k_2.

It is important to note that at any stage, we have the option to stop splitting. That is, at the first stage we may not split at all and return Ω as the partition. Moreover, at the second stage, we may choose to split within only one or even none of the subsets from the first stage. In this way, from two rounds of splitting, we may form 1, 2, 3, or 4 subsets of Ω. This procedure is naturally extensible to multiple rounds of splitting: given any subset, the splitting rule is simply to choose a biomarker and a threshold, and then to bisect the subset along the threshold. In this work, we limit ourselves to two rounds of splitting, as in the motivating AD trial. This constraint limits the incidence of subgroups containing relatively few patients.

Our construction of the partition has a natural structure: that of a tree. Let each node represent a subset of Ω, so that nodes with a common parent form a partition

of their parent. Moreover, every node has at most two children (we split each subset in two in each round). It follows that the final leaves of this tree are the sets $\{S_m\}$ that form the partition Π.

In Figure 1, we show an example with two continuous biomarkers supported on $[-1, 1]$ and two rounds of splits. We begin with $\Omega = [-1, 1]^2$ and then split Ω along biomarker 2 into two subsets: $L_2 = \{x_{i2} \leq 0\}$ and $U_2 = \{x_{i2} > 0\}$. We use the letter L to denote that the measurements are *lower* than the threshold, and U for *above* the threshold. In the second round of splits, we split U_2 into two subgroups UU_{21} and UL_{21} by splitting along biomarker 1 with threshold 0.7. We split L_2 into two further subgroups LU_{22} and LL_{22} by splitting further along biomarker 2 with threshold -0.5. The order of the letters U and L is chosen to match the order of the subscript indices. Hence, at the end, the partition $\Pi = \{UU_{21}, UL_{21}, LU_{22}, LL_{22}\}$, so that there are four subgroups.

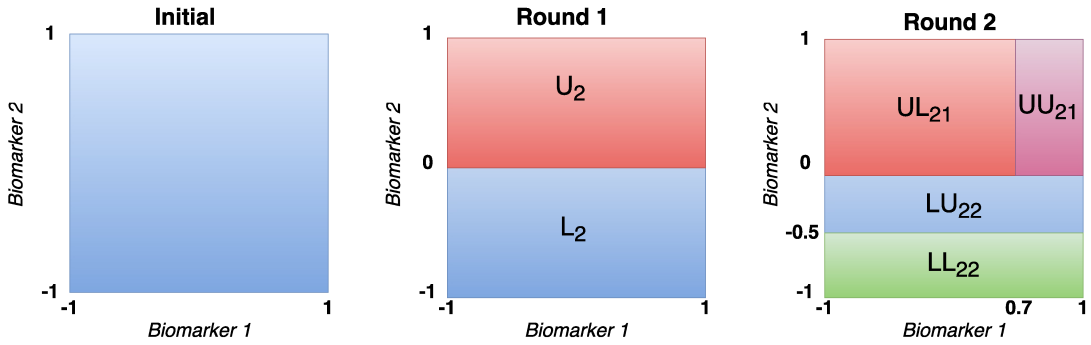

Figure 1: An illustration of Π. The example shows that with two rounds of splitting, the initial space of two biomarkers is partitioned into four subsets $\Pi = \{UU_{21}, UL_{21}, LU_{22}, LL_{22}\}$.

3 Trial Design

In this section, we discuss the trial design for a continuous outcome with two treatments (one placebo and one compound under investigation) and one interim analysis. While this setup mimics the motivating AD trial, we could easily extend our analysis to several treatments and several interim analyses, and to other response types.

The goal of the interim analysis is to learn which regions of the biomarker space Ω yield promising candidates for the compound under investigation. However, the partition is a random variable with a distribution. We must hence be creative in how we report our results. Assume that we have biomarker and response data from N patients, and let $\mathcal{D}_N = \{\boldsymbol{Y}_N, \boldsymbol{X}_N, \boldsymbol{Z}_N\}$ be the response, biomarker, and treatment data. Assume further that we have posterior samples of $\Pi^{(b)} = \{S_m^{(b)}\}_{m=1}^M$ from a Markov Chain Monte Carlo (MCMC) simulation. Next, we construct a grid in Ω. In each biomarker k, we let D_k be a finite, positive integer and choose D_k evenly spaced points in the domain of biomarker k. We then take the Cartesian product of these sets to yield the final grid. Then, each grid point d has a biomarker profile $\boldsymbol{x}_d$ given by its coordinates. From the MCMC data, we can iterate over the posterior samples $\Pi^{(b)}$ and assign d to a subgroup $S_m^{(b)}$. From the subgroup assignment, we may assign the response $\theta_{z_d,d}^{(b)}$ for point d under treatment z_d to the subgroup response under the same treatment, $\theta_{z_d,m}^{(b)}$. After repeating this procedure for each grid point and treatment, we have an array with values of θ for each grid point under each treatment from each posterior sample of Π.

We have assumed that $T = 2$, that is, that there are two treatments: placebo and an investigational compound. Let $q_d^{(b)} = \theta_{2,d}^{(b)} - \theta_{1,d}^{(b)}$ be the difference between the response under the compound and placebo. This quantity is the treatment effect. If there are B posterior samples (after burn-in, discarding, et cetera), we can approximate the posterior probability of a patient with biomarker profile $\boldsymbol{x}_d$ having

a treatment effect larger than or equal to some 'Low Reference Value' (LRV) by

$$\xi_d = \frac{1}{B}\sum_{b=1}^{B} I_{\{q_d^{(b)} \geq \text{LRV}\}},$$

where I_a is the indicator for the event a (taking value 1 if a occurs, and 0 otherwise). The LRV is a clinically given quantity, and is the minimum increment between two treatments' effects that is meaningful.

Now that we have specified the background information and notation, we describe how our trial, ASID, will be conducted.

1. The start of the trial. The first n patients are equally randomized to both treatment groups (placebo, investigational compound).

2. The interim analysis. Let Δ be the convex hull (smallest possible convex superset) of the set $\{d : \xi_d \geq \delta\}$ for some threshold δ (Graham, 1972).

    - If Δ is non-empty, we restrict the recruitment of new patients into the trial to patients with biomarker profiles $\boldsymbol{x}_i$ contained in Δ. We equally randomize the additional $N - n$ patients to both treatment groups.
    - If Δ is empty, we end the trial.

4 Simulation Studies

In this section, we perform numerical experiments to demonstrate the performance of our algorithm, ASID.

4.1 Simulation Setup

The setup herein mimics the motivating AD trial. Our goal is to evaluate the performance of the ASID relative to other methods. We simulate from $K = 4$ biomarkers and assume a uniform prior for splits on these biomarkers: $p(\nu_k) = 1/(K+1)$. The priors on the other parameters $\boldsymbol{c}$ are given in Appendix A. We assume that there is a initial phase with $n = 80$ patients, wherein all patients are equally and uniformly assigned to the placebo and compound under investigation. In every trial, the maximum sample size is capped at $N = 140$ patients.

We compare our method, ASID, with a linear regression (LR) model. In the LR setup, we model the responses with a Bayesian linear regression wherein we include all solo effects and the interactions between the treatment and biomarkers. That is,

$$y_i \mid z_i, \boldsymbol{x}_i = \beta_0 + \beta_1 z_i + \boldsymbol{\alpha}\boldsymbol{x}_i + \boldsymbol{\gamma} z_i \boldsymbol{x}_i + \epsilon_i, \tag{4.1}$$

where the ϵ_i are *i.i.d.* centered Gaussians with variance σ^2. We place non-informative conjugate priors on β and σ^2: β is given a multivariate normal prior with mean zero and covariance $20\mathcal{I}$, and σ^2 has an inverse Gamma prior with parameters $(0.1, 0.1)$. We use a Gibbs sampler to find posterior samples, from which we compute

$$q_d^{(b)} = E(y_i \mid z_i = 1, \boldsymbol{x}_d) - E(y_i \mid z_i = 0, \boldsymbol{x}_d).$$

We also compare our method with GUIDE (Loh et al., 2015). We fit a GUIDE random forest linear regression model 200 times for each set of patient data. Each constructed random forest is based on ten trees each and uses no more than three split levels. We let a patient's assigned treatment be considered a categorical variable

in an effort to use all biomarkers as well as the treatment assignment as variables for splitting. For an ensemble method such as random forest, GUIDE does not explicitly report subgroups, so we compute treatment effects over a grid.

We vary the LRV, the clinically meaningful threshold for the effect sizes. Note that 2.37 is the LRV that represents the average performance of marketed drugs, and an LRV above 2.37 indicates that there is a gain worth pursuing; 3.08 is the TRV, or the Targeted Reference Value for a new compound. For convenience, we use LRV for both LRV and TRV. Additionally, we vary both the stopping point in the enrichment design and the threshold δ for the minimum posterior probability of the treatment effect being larger than the LRV. When this occurs for a grid point with a particular biomarker profile $\boldsymbol{x}_d$, we say that this grid point belongs to the 'successful subgroup', that is, a latent subset of grid points (patients) who respond positively to the investigational compound.

4.2 Scenarios

There are six scenarios that we consider. These scenarios are depicted in Figure 2. The figure shows the regions where treatment 2 (the investigational compound) outperforms treatment 1 (the placebo). Note that there are $K = 4$ biomarkers: there are two additional biomarkers that we do not (and cannot) plot. We assume that these biomarkers have no bearing on the treatment outcome and that they are continuously valued with domain $[-1, 1]$.

Formally, we model the scenarios as follows. We let the response y_i be generated as follows:

$$y_i = \epsilon_i + \begin{cases} 0.75 & \text{if } z_i = 1, \\ 1.0 & \text{if } z_i = 2 \text{ and } \boldsymbol{x}_i \notin R_s \\ 1.0 + E & \text{if } z_i = 2 \text{ and } \boldsymbol{x}_i \in R_s, \end{cases}$$

where E is our effect size (set to 3.5) and R_s is the 'active region' for treatment 2 under scenario s. The phrase 'active region' refers to the region of the biomarker space where treatment 2 outperforms treatment 1. We use ϵ_i to denote a standard

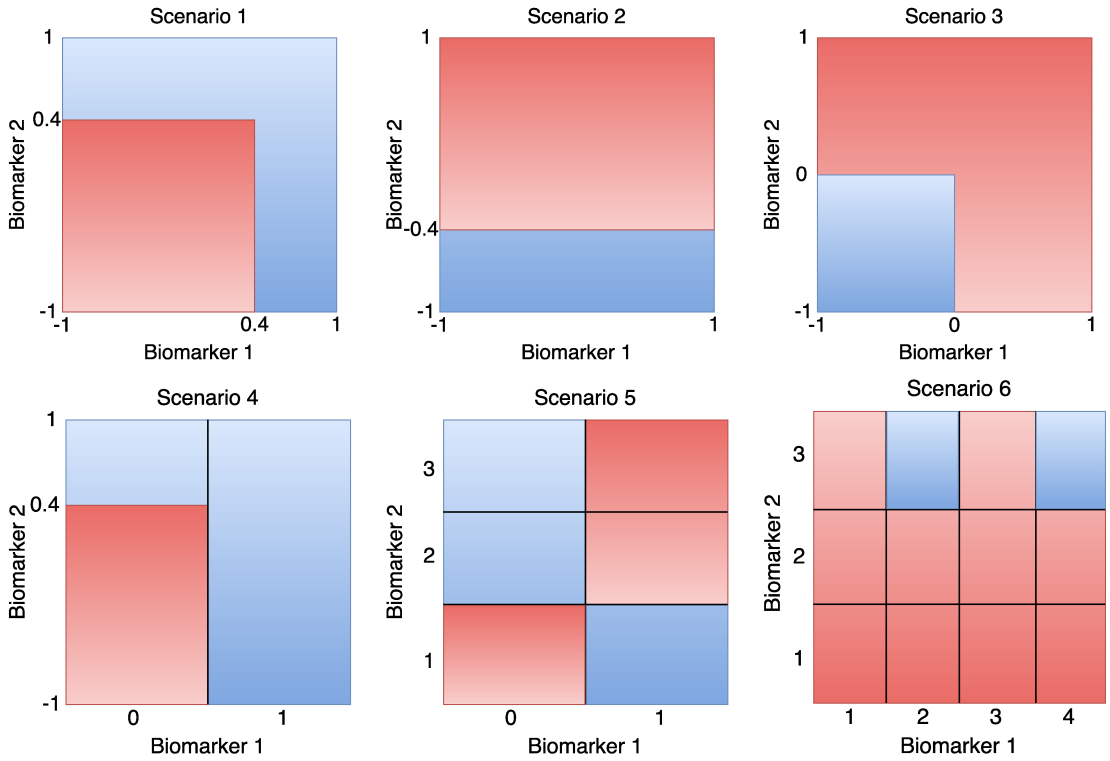

Figure 2: The six simulation truths: the color red represents regions wherein treatment 2 outperforms treatment 1. These are the 'active regions'.

Gaussian random variable (mean 0 and variance 1). The regions R_s are described in Table 1.

Scenario	Domain of x_1	Domain of x_2	R_s
1	$[-1, 1]$	$[-1, 1]$	$x_2 \leq 0.4$ and $x_1 \leq 0.4$
2	$[-1, 1]$	$[-1, 1]$	$x_2 \geq -0.4$
3	$[-1, 1]$	$[-1, 1]$	$x_2 \geq 0$, or, $x_2 < 0$ and $x_1 \geq 0$
4	$\{0, 1\}$	$[-1, 1]$	$x_2 \leq 0.4$ and $x_1 = 0$
5	$\{0, 1\}$	$\{1, 2, 3\}$	$x_2 = 1$ and $x_1 = 0$, or, $x_2 \in \{2, 3\}$ and $x_1 = 1$
6	$\{1, 2, 3, 4\}$	$\{1, 2, 3\}$	$x_1 = 1$, or, $x_1 = 3$, or, $x_2 \leq 2$ and $x_1 \in \{2, 4\}$

Table 1: The scenario truths and regions where treatment 2 outperforms treatment 1.

4.3 Simulation Metrics

Let ξ_d^h be the posterior probability that the treatment effect in trial h from grid point d with biomarker profile $\boldsymbol{x}_d$ is larger than the LRV. From 100 trials, we computed

$$\hat{\Delta} = \{d : \frac{1}{100} \sum_{h=1}^{100} \xi_d^h \geq \delta\},$$

where δ is the threshold for a success and is varied between 0 and 1.

Furthermore, we report the True Positive Rate (sensitivity) and the True Negative Rate (specificity) of the subgroups. We define:

$$TPR = \sum_{\{d:\boldsymbol{x}_d \in S^o\}} \sum_{h=1}^{100} I(\boldsymbol{x}_d \in \hat{\Delta})/(|S^o| \times 100),$$

where $|S^o|$ is the number of grid points in the simulated true effective subgroup; and

$$TNR = \sum_{\{d:\boldsymbol{x}_d \notin S^o\}} \sum_{h=1}^{100} I(\boldsymbol{x}_d \notin \hat{\Delta})/(|\Omega \setminus S^o| \times 100).$$

Note that the TPR and TNR are between 0 and 1, and in the ideal case are equal to 1.

Finally, we study the effect of enrichment in ASID. We compare modifying the study entry criteria at the interim analysis with not doing so (the WO design). Let y_i^h be the response and z_i^h be the treatment assignment for patient i in trial h. We define the overall mean treatment effect (OMT) as

$$\text{OMT} = \frac{1}{100}\sum_{h=1}^{100}\left(\frac{\sum_{i=n+1}^{N} y_i^h I(z_i^h = 2)}{\sum_{i=n+1}^{N} I(z_i^h = 2)} - \frac{\sum_{i=n+1}^{N} y_i^h I(z_i^h = 1)}{\sum_{i=n+1}^{N} I(z_i^h = 1)}\right).$$

This quantity is the average of the treatment effects between the two treatment groups after the interim analysis at the end of the trial. We want this value to be as large as possible. We compare the effect sizes from recruiting from all subgroups (ALL) with recruiting from only the subgroup wherein a significant treatment effect was detected (SUB).

Finally, we study whether under a truly null scenario, we recover a null result. We notate this by SFE (subgroup found error), and in the ideal case, it is equal to 0.

4.4 Results

We present our results in tabular form in Appendix H. Theses tables are separated first by scenario, and second by the value of the threshold δ. Within each table, we vary the number of patients and the LRV. All three methods are compared side-by-side. We also present figures for $\delta = 0.9$ and the LRV equal to 2.37 and 3.08.

The simply stated conclusion from these numbers and figures is that our method, ASID, outperforms GUIDE and a linear regression in the best case, and has performance comparable to that of GUIDE in the worst case. We go into detail about each metric below.

4.4.1 TPR

In Scenario 1, shown in Figure 3, ASID outperforms GUIDE for lower patient numbers, before GUIDE 'catches up' at 140 patients. In Scenario 2, shown in Figure 4, ASID and GUIDE are comparable for low LRV, but ASID noticeably outperforms GUIDE for high LRV. In Scenario 3, shown in Figure 5, we have the same trend as in Scenario 2. In Scenario 4, shown in Figure 6, ASID outperforms GUIDE for low patient sizes. Interestingly, GUIDE appears to exhibit a phase transition type behavior as the number of patients increases. In Scenario 5, shown in Figure 7, ASID outperforms GUIDE. Finally, in Scenario 6, shown in Figure 8, ASID and GUIDE are generally comparable. In all Scenarios, the linear regression (LR) performs worse than ASID and GUIDE.

4.4.2 TNR

The TNR values for all algorithms and LRV values are comparable and close to 1, except in Scenario 3, shown in Figure 5. The ASID TNR values lag behind both those of GUIDE and the linear regression for smaller patient sizes, and are closer but still lower at higher patient sizes.

4.4.3 SFE

The SFE for all algorithms and LRV values is essentially zero.

4.4.4 Effect Sizes

The last comparison we make is that of the effect sizes under enriched v. non-enriched scenarios. In Scenario 1, shown in Figure 3, the enrichment design leads to a higher effect size for all patient sizes and algorithms. In Scenario 2 (Figure 4), 3 (Figure 5), 4 (Figure 6), and 5 (Figure 7), we have the same result. In Scenario 6, shown in Figure 8, the effect size values from the enrichment are greater than those from without the enrichment, except for a few patient sizes with the GUIDE algorithm. The margin is also smaller in Scenario 6.

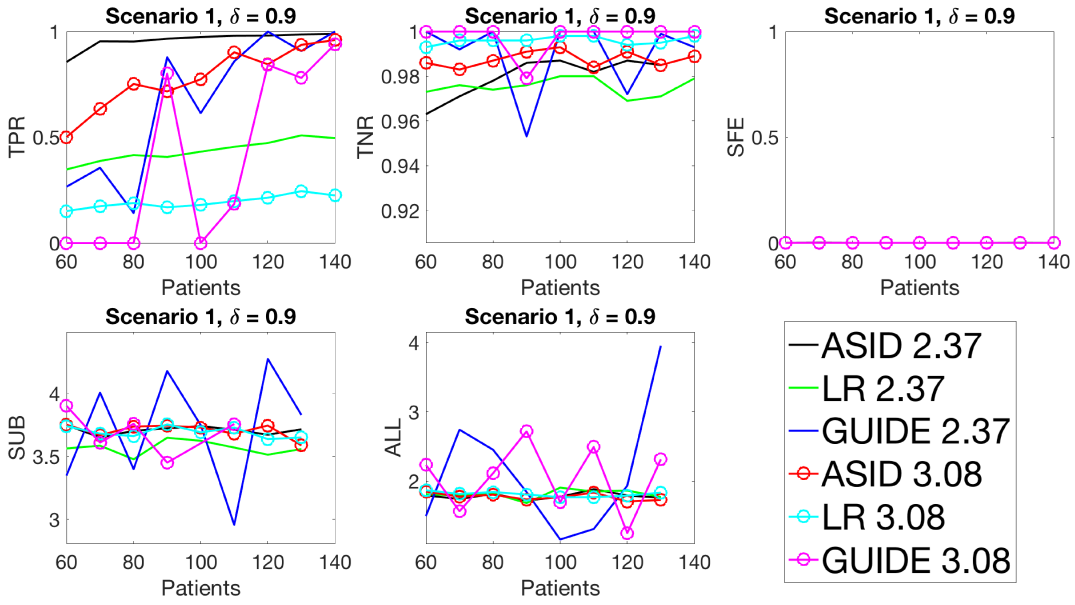

Figure 3: Scenario 1 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

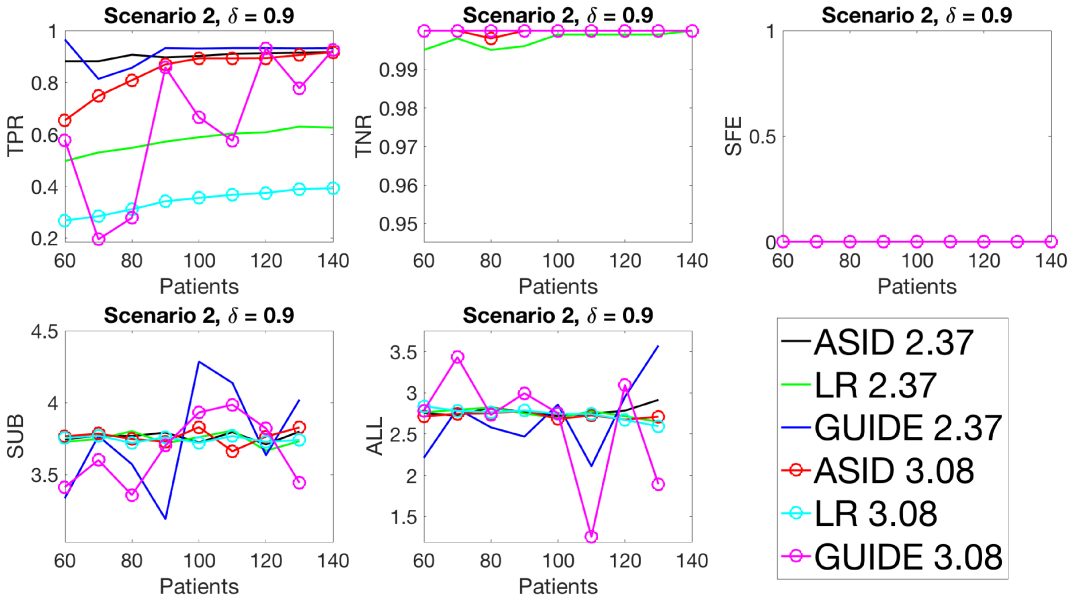

Figure 4: Scenario 2 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

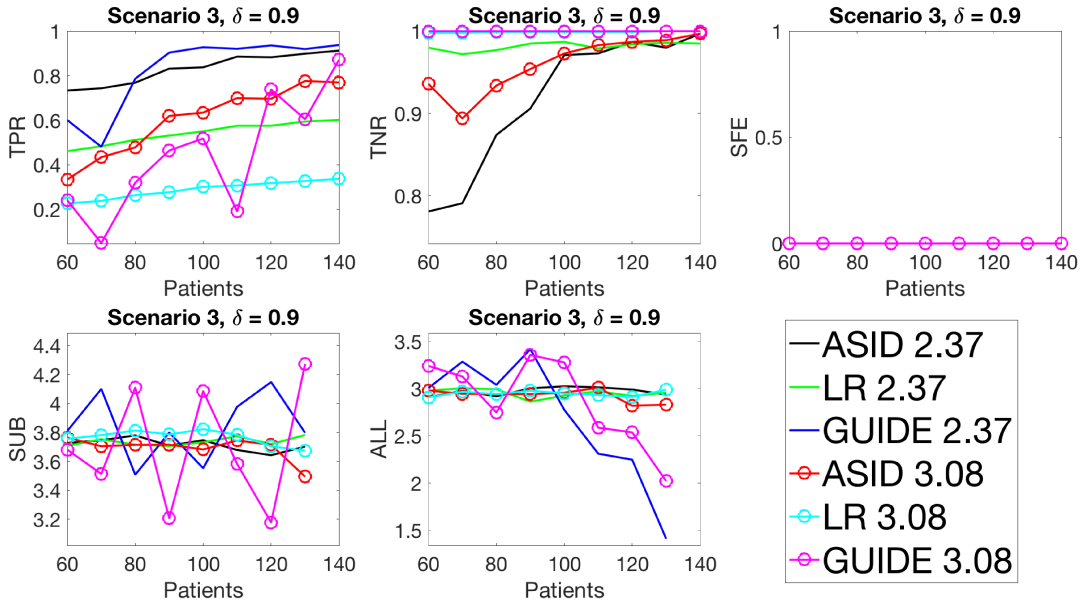

Figure 5: Scenario 3 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

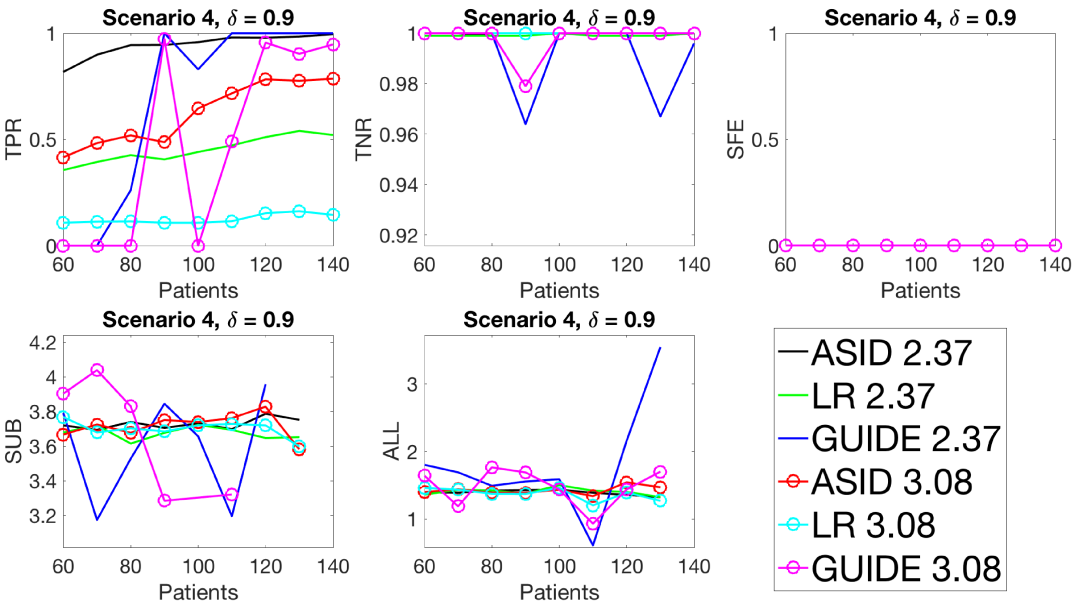

Figure 6: Scenario 4 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

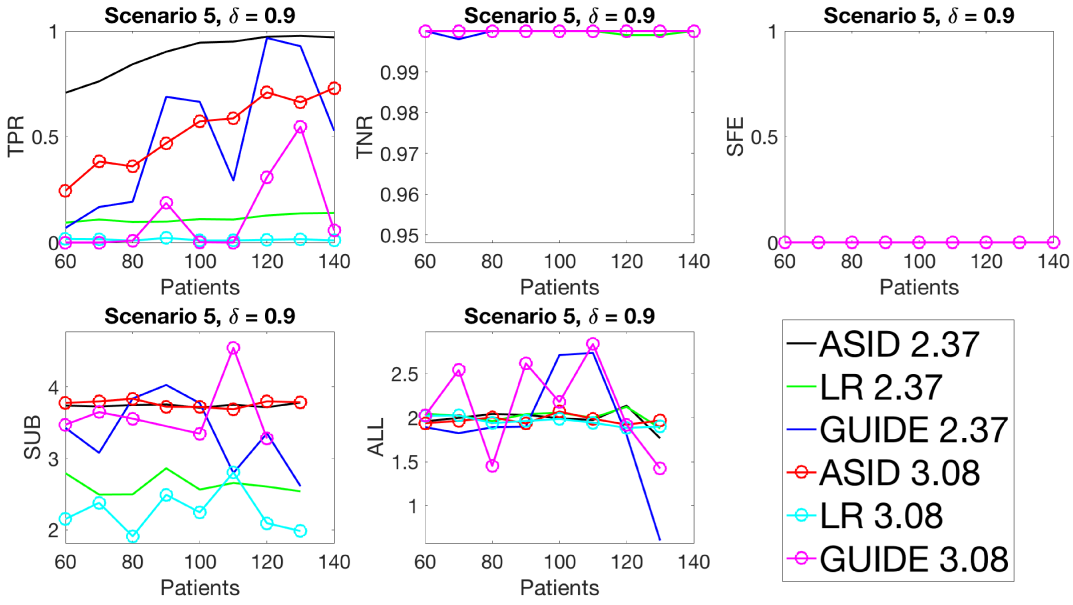

Figure 7: Scenario 5 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

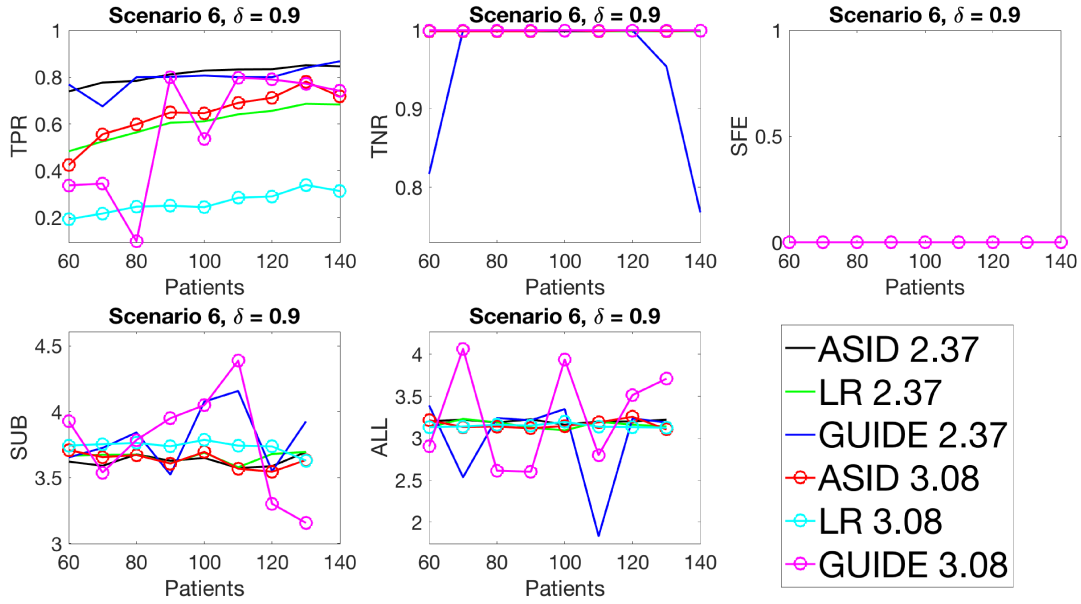

Figure 8: Scenario 6 results, $\delta = 0.9$ and $LRV = 2.37$ and 3.08.

5 Conclusion

In this thesis, we have proposed, derived, implemented, tested, and analyzed a novel method for clinical trial design. Our method is adaptive and is an enrichment design. Additionally, it is built around a hierarchical Bayesian model. The method allows for adaptive identification of subgroups with differential treatment effects, and adaptive modification of trial entry criteria. One key contribution of our method, ASID, is the random partition model and an MCMC algorithm for sampling from the posterior distribution of this model.

The principal takeaway of this work is demonstrated conclusively in the numerical simulations. ASID effectively and successfully recovers the subgroups depicted in the simulation truth, and relative to GUIDE and a linear regression design, has stronger statistical performance.

Future work on this project would extend ASID to the scenario where there are many biomarkers, and variable selection must be performed at each stage. Additionally, a simple extension would include an adaptive patient allocation scheme, wherein patients would be assigned to their optimal treatments, and a 'favorable' or 'optimal' patient subgroup to recruit from for a later phase III trial would be specified.

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Appendix A Partition

In this section, we describe the rules for forming a partition of the biomarker space Ω. We assume that there are two rounds of splits, and that the covariates may have continuous, binary, categorical, or ordinal domains. We assume that there are K biomarkers, indexed by $\{1, \ldots, K\}$, and that the letter k is used to index biomarkers. The letter c will be used to index the thresholds or split locations. We will use $\boldsymbol{x}_i$ to denote an arbitrary biomarker vector with k^{th} coordinate $\boldsymbol{x}_{ik}$.

A.1 The First Split

We first choose a biomarker k to split on. We assume that we choose a biomarker k with probability $\nu_k = 1/(K+1)$, and that we may choose not to split with probability $\nu_0 = \nu_k$. That is, there is a uniform prior on k. We next choose the location of the split c_k, so that we split the biomarker space Ω into two subsets, L_k and U_k.

- If we choose not to split, we are done: c_k is irrelevant. We may set $c_k = \emptyset$, and assume by convention that $p(c_k \mid k) = 1$.

- If the biomarker k is binary valued, the split is deterministically given: there is only one option. We let $L_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} = 0\}$ and $U_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} = 1\}$, and $p(c_k \mid k) = 1$.

- If the biomarker k is continuous, we let $L_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} \leq c_k\}$ and $U_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} > c_k\}$. We let $p(c_k \mid k)$ be uniformly distributed on the observed domain of biomarker k, that is, Uniform$(\min\{\boldsymbol{x}_{ik}\}_{i=1}^N, \max\{\boldsymbol{x}_{ik}\}_{i=1}^N)$. If the support of biomarker k is $[-1, 1]$, $p(c_k \mid k) = 1/2$.

- If the biomarker k is ordinal valued, let V_k be the number of distinct values of biomarker k, where the set of values is $\{1, \ldots, V_k\}$. Let c_k denote the endpoint of the 'left' partition, i.e., $L_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} \leq c_k\}$ and $U_k = \{\boldsymbol{x}_i : \boldsymbol{x}_{ik} > c_k\}$. We constrain c_k to be smaller than V_k: if $c_k = V_k$, we are not splitting, which

is a previously considered event. We assume a uniform prior on c_k, where $p(c_k \mid k) = 1/(V_k - 1)$. Note that if V_k is 2, we are exactly in the binary setting.

- If the biomarker k takes discrete values without any further structure, we say that it is a categorical variable. Let this variable take values in the set $C_k = \{1, \ldots, V_k\}$. We will use c_k to represent one subset of C_k, so that $L_k = c_k$ and U_k is the complement of c_k, or $C_k \backslash c_k$. Note that if c_k is equal to $\emptyset$ or C_k, we are not splitting. Hence, c_k is valued in the powerset of C_k, without the elements $\emptyset$ and C_k. Thus, if we choose a uniform prior for c_k, $p(c_k \mid k) = 2/(2^{V_k} - 2)$. The extra factor of 2 comes from the symmetry between L_k and U_k: choosing c_k or its complement leads to the same partition.

A.2 The Second Split

We now discuss the second split. If we do not split in the first round, there is no second split. If we do split in the first round, we have two subsets: L_k and U_k. We split again within each subset. There is also the option of not splitting within one or both subsets. Assuming that we split within both subsets, we choose biomarker k_1 for the split within L_k and k_2 for that within U_k, and give both the same priors as k. If we split within L_k, we choose a threshold c_{k_1} to form LL_{k,k_1} and LU_{k,k_1}. Similarly, we form UL_{k,k_2} and UU_{k,k_2} using threshold c_{k_2}.

We now discuss how to form c_{k_1} and c_{k_2}. We describe the structure of the subsets, and then describe the priors.

- No split:
  1. If we do not split within L_k, $c_{k_1} = \emptyset$ and we say that $p(c_{k_1} \mid k, k_1) = 1$.
  2. If we do not split within U_k, $c_{k_2} = \emptyset$ and we say that $p(c_{k_2} \mid k, k_2) = 1$.
- Binary Biomarkers:
  1. If biomarker k_1 is a binary valued variable, let $LL_{k,k_1} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in L_k, \text{ and } x_{ik_1} = 0\}$ and $LU_{k,k_1} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in L_k, \text{ and } \boldsymbol{x}_{ik_1} = 1\}$ with $p(c_{k_1} \mid k, k_1, c_k) = 1$.

2. If biomarker k_2 is a binary valued variable, let $UL_{k,k_2} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in U_k, \text{ and } \boldsymbol{x}_{ik_2} = 0\}$ and $UU_{k,k_2} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in U_k, \text{ and } \boldsymbol{x}_{ik_2} = 1\}$ with $p(c_{k_2} \mid k, k_2, c_k) = 1$.

3. Note that $k = k_1$ or $k = k_2$ are nonsensical options here.

- Continuous Biomarkers:

1. If biomarker k_1 is continuous and $k \neq k_1$, let $LL_{k,k_1} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in L_k \text{ and } \boldsymbol{x}_{ik_1} \leq c_{k_1}\}$ and $LU_{k,k_1} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in L_k \text{ and } \boldsymbol{x}_{ik_1} > c_{k_1}\}$. We have that $p(c_{k_1} \mid k, k_1, c_k)$ is uniform on the domain of biomarker k_1. If the support of biomarker k_1 is $[-1, 1]$, $p(c_{k_1} \mid k, k_1, c_k) = 1/2$.

2. If biomarker k_1 is continuous and $k = k_1$, the above setup holds, but $p(c_{k_1} \mid k, k_1, c_k)$ is uniform on the range of L_k, that is $\{\boldsymbol{x}_i : \boldsymbol{x}_i \leq c_k\}$. If the support of biomarker k is $[-1, 1]$, $p(c_{k_1} \mid k, k_1, c_k) = 1/(1 + c_k)$.

3. If biomarker k_2 is continuous and $k \neq k_2$, let $UL_{k,k_2} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in U_k \text{ and } x_{ik_2} \leq c_{k_2}\}$ and $UU_{k,k_2} = \{\boldsymbol{x}_i : \boldsymbol{x}_i \in U_k \text{ and } x_{ik_2} > c_{k_2}\}$. We have that $p(c_{k_2} \mid k, k_2, c_k)$ is uniform on the domain of biomarker k_2. If the support of biomarker k_2 is $[-1, 1]$, $p(c_{k_2} \mid k, k_2, c_k) = 1/2$.

4. If biomarker k_2 is continuous and $k = k_2$, the above setup holds, but $p(c_{k_2} \mid k, k_2, c_k)$ is uniform on the range of U_k, that is $\{\boldsymbol{x}_i : \boldsymbol{x}_i > c_k\}$. If the support of biomarker k is $[-1, 1]$, $p(c_{k_2} \mid k, k_2, c_k) = 1/(1 - c_k)$.

- Ordinal Biomarkers:

1. If biomarker k_1 takes ordinal values and $k \neq k_1$, let c_{k_1} denote the left endpoint of the second split within L_k. We have a uniform prior $p(c_{k_1} \mid k, k_1, c_k) = \frac{1}{V_{k_1} - 1}$. We form LL_{k,k_1} and LU_{k,k_1} analogously to how L_k and U_k were formed.

2. If biomarker k_1 takes ordinal values and $k = k_1$, the above holds, except that $p(c_{k_1} \mid k, k_1, c_k) = \frac{1}{c_k - 1}$.

3. If biomarker k_2 is ordinal valued and $k \neq k_2$, let c_{k_2} denote the left endpoint of the second split within U_k. Then, $p(c_{k_2} \mid k, k_2, c_k) = \frac{1}{V_{k_2}-1}$ and we form UL_{k,k_2} and UU_{k,k_2} analogously to how L_k and U_k were formed.

4. If biomarker k_2 takes ordinal values and $k = k_2$, the above holds, except that $p(c_{k_2} \mid k, k_2, c_k) = \frac{1}{V_k - c_k - 1}$.

- Categorical Biomarkers:

1. If biomarker k_1 takes categorical values and $k \neq k_1$, let c_{k_1} denote the left subset of the second split within L_k. We have a uniform prior $p(c_{k_1} \mid k, k_1, c_k) = \frac{2}{2^{V_{k_1}}-2}$, exactly as we did on c_k. We form LL_{k,k_1} and LU_{k,k_1} analogously to how L_k and U_k were formed.

2. If biomarker k_1 takes categorical values and $k = k_1$, the above holds, except that $p(c_{k_1} \mid k, k_1, c_k) = \frac{2}{2^{|c_k|}-2}$, where $|A|$ denotes the cardinality of the set A.

3. If biomarker k_2 is categorically valued and $k \neq k_2$, let c_{k_2} denote the left subset of the second split within U_k. Then, $p(c_{k_2} \mid k, k_2, c_k) = \frac{2}{2^{V_{k_2}}-2}$ and we form UL_{k,k_2} and UU_{k,k_2} analogously to how L_k and U_k were formed.

4. If biomarker k_2 takes categorical values and $k = k_2$, the above holds, except that $p(c_{k_2} \mid k, k_2, c_k) = \frac{2}{2^{V_k - |c_k|}-2}$.

Appendix B A Combinatorial Aspect of Subgroup Generation

For $x \neq 1$ and a non-negative integer r, we have that

$$\sum_{k=0}^{r} x^k = 1 + x + x^2 + \cdots + x^r = \frac{x^{r+1} - 1}{x - 1}.$$

This is an elementary combinatorial identity for the partial sums of a geometric series. Interestingly, this identity has a natural connection to our method of obtaining subgroups and creating the partitions described in Appendix A.

Let there be N biomarkers and at most r rounds of splits. Our claim is that the quantity

$$1 + (2N) + (2N)^2 + \cdots + (2N)^r = \sum_{k=0}^{r} (2N)^k = \frac{(2N)^{r+1} - 1}{(2N) - 1}$$

is the number of possible subgroups modulo the thresholds. That is, if we solely characterize subgroups by which variables were split on and whether they are greater than or less than some threshold, this quantity is the number of possible subgroups.

Before delving into the justification of our claim, we given an example to explain what we mean by subgroups modulo thresholds. Our notation to label the subgroups is as follows. We will use the number $(N + 1)$ to indicate that we do not split in a given round. Following a biomarker index, we will use 0 to indicate the left (below the threshold) subgroup and 1 to indicate the right (above the threshold) subgroup; after $(N + 1)$, we use $(N + 1)$ in place of 0 or 1. Our example has $N = 2$ continuous biomarkers. If we do not split, we have the whole space as a single subgroup, which we notate by 33. If we split along biomarker 2 and then do not split further, we have two subgroups: 20 and 21. If we split along biomarker 2, and then in the 'left' section split again along biomarker 2 and split along biomarker 1 in the 'right' section, we have 4 subgroups. The subgroups are labeled by 2020 (left within left), 2021 (right

within left), 2110 (left within right), and 2111 (right within right). Figure 9 displays this construction.

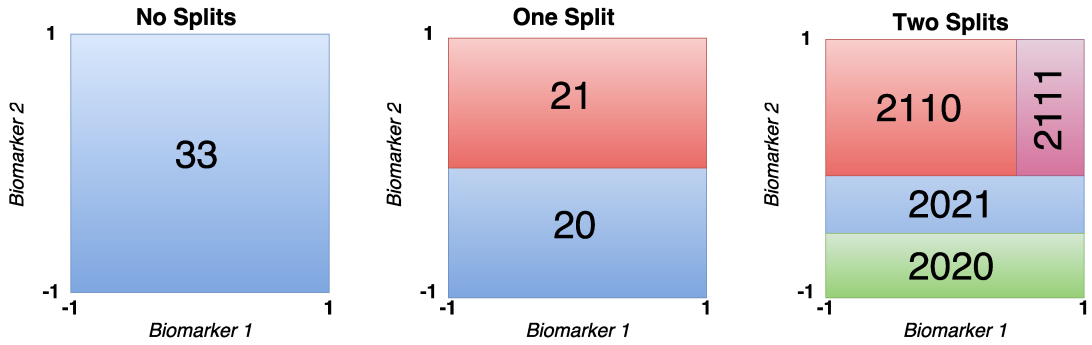

Figure 9: An illustration of a set of possible subgroups and our notation from no, one, and two rounds of splitting with two biomarkers.

We reason inductively to find our conclusion. If we do not split ($r = 0$), there is only one subgroup. If we split once ($r = 1$), there are N choices for biomarkers. For each choice of biomarker, we may choose to take the 'left' or 'right' subgroup, so that there are $2N$ choices. Assume now that we have split $r - 1$ times and have some number of subgroups. Within each subgroup, we may make exactly one split (or none, but this case is covered by $r - 1$ rounds of splits, since if we do not split further, there simply are not r rounds). There are once again N biomarkers that we may split on, and for each choice, there is a 'left' and 'right' subgroup. Hence, there are $2N$ choices for each subgroup; we inductively assume that there are $(2N)^{r-1}$ choices from $r - 1$ rounds of splits. There are hence $(2N) \times (2N)^{r-1} = (2N)^r$ choices from r rounds of splits. It follows that from at most r rounds of splits, there are $1 + (2N) + \cdots + (2N)^r$ possible subgroups, as claimed.

We may also reason via our notation system. If we generate a subgroup from r splits, we have a string with $2r$ characters. There are N options for the first character, and 2 for the second. Then, there are N more options for the third, and 2 for the fourth, etc. Considering the total number of possibilities leads to $(2N)^r$ possible strings. Noting that there are up to r splits yields the desired summation.

We conclude with a brief remark about our notation system. When using this system in computer code, it may be inconvenient to have strings or numbers of differing

length. Hence, if we know that there are at most r rounds of splits, we may pad our character strings with $(N+1)$s so that all subgroups have labels of length $2r$.

Appendix C Binary Response Model

In this section, we report the details of the model for patients with a binary response.

We begin with some notation. Let n denote the total number of patients. Let n_{mt} denote the number of patients in subgroup m receiving treatment t. Let n_{mt1} be the number of patients in subgroup m receiving treatment t with response 1, and similarly for n_{mt0}. Let $\boldsymbol{Y}_n$ denote the collection of all patient responses Y_i. Note that the Y_i's are independent. Similarly, let $\boldsymbol{X}_n$ and $\boldsymbol{Z}_n$ denote the collection of all biomarker profiles X_i and treatment indices Z_i, respectively. Let $\theta_{t,m}$ be the response rate of patients in subgroup m under treatment t and let $\boldsymbol{\theta}$ denote the collection of all $\theta_{t,m}$. We will use $\Gamma(x)$ to denote the Gamma function evaluated at x.

C.1 Likelihood

Since the response for all patients is binary, the likelihood is extremely simple:

$$p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\theta}, \boldsymbol{\Pi}) = \prod_t \prod_m \theta_{t,m}^{n_{mt1}} (1-\theta_{t,m})^{n_{mt0}}. \tag{C.1}$$

C.2 Prior for $\theta_{t,m}$

The conjugate prior for $\theta_{t,m}$ is a Beta distribution with shape parameters a, b:

$$p(\theta_{t,m} \mid \boldsymbol{\Pi}) = \text{beta}(\theta_{t,m}; a, b). \tag{C.2}$$

C.3 Posterior for $\theta_{t,m}$

The posterior distribution for $\theta_{t,m}$ is also a Beta distribution.

$$\begin{aligned} p(\theta_{t,m} \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\Pi}) &\propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\theta}, \boldsymbol{\Pi})\, p(\boldsymbol{\theta} \mid \boldsymbol{\Pi}) \\ &\propto \theta_{t,m}^{nmt1} (1-\theta_{t,m})^{nmt0} \cdot \text{beta}(\theta_{t,m}; a, b) \\ &\propto \theta_{t,m}^{nmt1} (1-\theta_{t,m})^{nmt0} \cdot \theta_{t,m}^{a-1} (1-\theta_{t,m})^{b-1} \end{aligned}$$

$$\propto \theta_{t,m}^{nmt1+a-1}(1-\theta_{t,m})^{nmt0+b-1}$$

$$\propto \text{beta}(nmt1+a, nmt0+b)$$

C.4 Posterior for Π

We now report the posterior for the partition Π. There is a nice, closed form expression that we find.

$$\begin{aligned}
p(\Pi \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n) &= p(\Pi) \int p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\theta}, \boldsymbol{\Pi})\, p(\boldsymbol{\theta} \mid \boldsymbol{\Pi})\, d\boldsymbol{\theta} \\
&= p(\Pi) \int_0^1 \cdots \int_0^1 [\prod_t \prod_m \theta_{t,m}^{n_{mt1}}(1-\theta_{t,m})^{n_{mt0}} \cdot \text{beta}(\theta_{t,m}; a, b)\, d\theta_{t,m}] \\
&= p(\Pi) \prod_t \prod_m \int_0^1 \theta_{t,m}^{n_{mt1}}(1-\theta_{t,m})^{n_{mt0}} \cdot \text{beta}(\theta_{t,m}; a, b)\, d\theta_{t,m} \\
&= p(\Pi) \prod_t \prod_m \int_0^1 \theta_{t,m}^{n_{mt1}}(1-\theta_{t,m})^{n_{mt0}} \cdot \frac{\Gamma(a+b)}{\Gamma(a)\,\Gamma(b)} \theta_{t,m}^{a-1}(1-\theta_{t,m})^{b-1}\, d\theta_{t,m} \\
&= p(\Pi) \prod_t \prod_m \frac{\Gamma(a+b)}{\Gamma(a)\,\Gamma(b)} \int_0^1 \theta_{t,m}^{n_{mt1}+a-1}(1-\theta_{t,m})^{n_{mt0}+b-1}\, d\theta_{t,m} \\
&= p(\Pi) \prod_t \prod_m \frac{\Gamma(a+b)}{\Gamma(a)\,\Gamma(b)} \cdot \frac{\Gamma(nmt1+a)\,\Gamma(nmt0+b)}{\Gamma(a+b+nmt1+nmt0)}
\end{aligned}$$

Appendix D Categorical Response Model

In this section, we report the details of the model for patients with a categorical response.

We begin with some notation. Let n denote the total number of patients. Let there be C possible outcomes. Let n_{mt} denote the number of patients in subgroup m receiving treatment t. Let n_{mtc} be the number of patients in subgroup m receiving treatment t with response c. Let $\boldsymbol{Y}_n$, $\boldsymbol{X}_n$, and $\boldsymbol{Z}_n$ denote the collection of all patient responses Y_i, biomarker profiles X_i, and treatment indices Z_i, respectively. Note that the Y_i's are independent. Let $\theta_{c,t,m}$ be the response rate of patients in subgroup m under treatment t with outcome c and let $\boldsymbol{\theta}$ denote the collection of all $\theta_{c,t,m}$. We will use $\Gamma(x)$ to denote the Gamma function evaluated at x.

D.1 Likelihood

Since the response for all patients is categorical, the likelihood is extremely simple:

$$p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\theta}, \boldsymbol{\Pi}) = \prod_t \prod_m \prod_c \theta_{c,t,m}^{n_{mtc}} \tag{D.1}$$

D.2 Prior for $\theta_{c,t,m}$

The conjugate prior for $\theta_{c,t,m}$ is a Dirichlet distribution with parameter $a = (a_1, \cdots, a_C)$, where $a_c > 0$ for $c \in \{1, \cdots, C\}$. We notate this by $\text{Dir}(C, a)$.

D.3 Posterior for $\theta_{c,t,m}$

The posterior distribution for $\theta_{c,t,m}$ is also a Dirichlet distribution: let $\kappa = (n_{mt1}, \cdots, n_{mtC})$. Then the posterior for $\theta_{c,t,m} = (\theta_{1,t,m}, \cdots, \theta_{C,t,m})$ is $\theta_{c,t,m} \sim \text{Dir}(C, a+\kappa)$. The derivation of this fact is found in a similar manner to the derivation done to find the posterior of $\theta_{t,m}$ for a binary response in Appendix C.

D.4 Posterior for Π

We now report the posterior for the partition Π.

$$\begin{aligned} p(\Pi \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n) &= p(\Pi) \cdot \int p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \boldsymbol{\theta}, \boldsymbol{\Pi})\, p(\boldsymbol{\theta} \mid \boldsymbol{\Pi}) d\boldsymbol{\theta} \\ &= p(\Pi) \int [\prod_{m,t} \prod_{c} \theta_{c,t,m}^{n_{mtc}} \cdot \mathrm{Dir}(\theta_{t,m}; C, a) d\theta_{t,m}], \end{aligned}$$

where the integration is over the simplex of non-negative $\theta_{c,t,m}$ summing to 1. Then, we may write this as

$$\begin{aligned} p(\Pi \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n) &= p(\Pi) \prod_{t} \prod_{m} \int \prod_{c} \theta_{c,t,m}^{n_{mtc}} \cdot \mathrm{Dir}(\theta_{t,m}; C, a) d\theta_{t,m} \\ &= B(a)^{-MT} \cdot p(\Pi) \prod_{t} \prod_{m} \int \prod_{c} \theta_{c,t,m}^{n_{mtc}+a_c-1} d\theta_{t,m}, \end{aligned}$$

where there are M subgroups with $m \in \{1, \ldots, M\}$, T treatments with $t \in \{1, \ldots, T\}$, and $B(a)$ is the normalizing constant of the Dirichlet distribution $\mathrm{Dir}(C, a)$:

$$B(a) = \frac{\prod_{c=1}^{C} \Gamma(a_c)}{\Gamma(\sum_{c=1}^{C} a_c)}.$$

This expression simplifies to

$$\begin{aligned} p(\Pi \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n) &= B(a)^{-MT} \cdot p(\Pi) \prod_{t} \prod_{m} \int \prod_{c} \theta_{c,t,m}^{n_{mtc}+a_c-1} d\theta_{t,m} \\ &= B(a)^{-MT} \cdot p(\Pi) \prod_{m,t} \frac{\prod_c \Gamma(n_{mtc} + a_c)}{\Gamma(n_{mt} + \sum_c a_c)}, \end{aligned}$$

which we may write as

$$p(\Pi \mid \boldsymbol{Y}_n, \boldsymbol{X}_n, \boldsymbol{Z}_n) = p(\Pi) \cdot \prod_{m,t} \left[\left(\frac{\Gamma(\sum_{c=1}^{C} a_c)}{\prod_{c=1}^{C} \Gamma(a_c)} \right) \cdot \frac{\prod_{c=1}^{C} \Gamma(n_{mtc} + a_c)}{\Gamma(n_{mt} + \sum_{c=1}^{C} a_c)} \right].$$

Note that this expression simplifies to the binary case when $C = 2$.

Appendix E Normal Response Model

In this section, we report the details of the model for patients with a continuous, normal response.

We begin with some notation. Let n denote the total number of patients. Let n_{mt} denote the number of patients in subgroup m receiving treatment t. Let $Y_{i;t,m}$ denote the i^{th} patient's response out of the subset of patients that belong to subgroup m and receive treatment t. Note that the Y_i's are independent. Let $\theta_{t,m}$ be the average response of patients in subgroup m under treatment t. We will use $\mathcal{N}(a, b)$ to denote a Gaussian distribution with mean a and variance b, and $IG(a, b)$ to denote an inverse Gamma distribution with mean b/a. Moreover, a subscript 0 on a parameter indicates that said parameter is a hyperparameter. Let $\boldsymbol{Y}_n$ and $\boldsymbol{\theta}$ denote the collection of all $Y_{i;t,m}$ and $\theta_{t,m}$, respectively.

We have that,

$$Y_{i;t,m} = \theta_{t,m} + \epsilon_i, \tag{E.1}$$

where $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$. Furthermore,

$$p(Y_{i;t,m} \mid \theta_{t,m}, \sigma^2) = (2\pi\,\sigma^2)^{-1/2} \exp\{-\frac{1}{2\sigma^2}(Y_{i;t,m} - \theta_{t,m})^2\} \tag{E.2}$$

E.1 Likelihood

We compute and simplify the likelihood below:

$$\begin{aligned}
p(\boldsymbol{Y}_n \mid \boldsymbol{\theta}, \sigma^2) &= \prod_{t=1}^{T} \prod_{m=1}^{M} \prod_{i \in S_m, z_i = t} p(Y_{i;t,m} \mid \theta_{t,m}, \sigma^2) \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{t}^{T} \sum_{m}^{M} \sum_{i \in S_m, z_i = t} (Y_{i;t,m} - \theta_{t,m})^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} (Y_{i;t,m} - \theta_{t,m})^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} (Y_{i;t,m} - \overline{Y}_{i;t,m} + \overline{Y}_{i;t,m} - \theta_{t,m})^2\}
\end{aligned}$$

$$
\begin{aligned}
&\text{where } \overline{Y}_{i;t,m} = \sum_{i,t,m} \frac{Y_{i;t,m}}{n} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} [(Y_{i;t,m} - \overline{Y}_{i;t,m}) - (\theta_{t,m} - \overline{Y}_{i;t,m})]^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} [(Y_{i;t,m} - \overline{Y}_{i;t,m})^2 + (\theta_{t,m} - \overline{Y}_{i;t,m})^2]\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} (\sum_{i,t,m} [(Y_{i;t,m} - \overline{Y}_{i;t,m})^2] + n(\theta_{t,m} - \overline{Y}_{i;t,m})^2)\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} [(Y_{i;t,m} - \overline{Y}_{i;t,m})^2] - \\
&\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} (Y_{i;t,m} - \overline{Y}_{i;t,m})^2\} \exp\{-\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} \frac{(Y_{i;t,m} - \overline{Y}_{i;t,m})^2}{n-1} (n-1)\} \\
&\exp\{-\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} s^2(n-1)\} \exp\{-\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&\text{where } s^2 = \sum_{i,t,m} \frac{(Y_{i;t,m} - \overline{Y}_{i;t,m})^2}{n-1} \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} SS\} \exp\{-\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&\text{where } SS = s^2(n-1) \\
&= (2\pi\,\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} SS\} \exp\{-\frac{1}{2\sigma^2} n(\theta_{t,m} - \overline{Y}_{i;t,m})^2\} \\
&\text{where } SS = \sum_{i,t,m} (Y_{i;t,m} - \overline{Y}_{i;t,m})^2.
\end{aligned}
$$

E.2 Priors

We have that the conjugate prior

$$p(\theta_{t,m}, \sigma^2) = p(\theta_{t,m} \mid \sigma^2)\, p(\sigma^2).$$

We now specify $p(\theta_{t,m} \mid \sigma^2)$ and $p(\sigma^2)$ where

$$p(\theta_{t,m} \mid \sigma^2) = \mathcal{N}(\theta_0, \frac{\sigma^2}{\kappa_0})$$

and $p(\sigma^2) = IG(\frac{\nu_0}{2}, \frac{SS_0^2}{2})$ with $SS_0^2 = \nu_0\sigma_0^2$. More explicitly:

$$\begin{aligned} p(\theta_{t,m} \mid \sigma^2) &= (2\pi\frac{\sigma^2}{\kappa_0})^{-1/2} \exp\{-\frac{1}{2\frac{\sigma^2}{\kappa_0}}(\theta_{t,m} - \theta_0)^2\} \\ &= (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2} \exp\{-\frac{\kappa_0}{2\sigma^2}(\theta_{t,m} - \theta_0)^2\}, \end{aligned}$$

and

$$\begin{aligned} p(\sigma^2) &= \frac{(\frac{SS_0^2}{2})^{\frac{\nu_0}{2}}}{\Gamma(\frac{\nu_0}{2})}(\sigma^2)^{-\frac{\nu_0}{2}-1} \exp\{\frac{-\frac{SS_0^2}{2}}{\sigma^2}\} \\ &= \frac{(\frac{SS_0^2}{2})^{\frac{\nu_0}{2}}}{\Gamma(\frac{\nu_0}{2})}(\sigma^2)^{-\frac{\nu_0}{2}-1} \exp\{-\frac{SS_0^2}{2\sigma^2}\}. \end{aligned}$$

E.3 Joint Model

Packaging the above expressions together, we may write the joint model as:

$$p(\boldsymbol{Y}_n, \boldsymbol{\theta}, \sigma^2, \Pi) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{\theta}, \sigma^2, \Pi)\, p(\boldsymbol{\theta} \mid \Pi)\, p(\sigma^2)\, p(\Pi \mid \boldsymbol{c})\, p(\boldsymbol{c}),$$

where $p(\boldsymbol{c}) = p(k)\, p(k_1)\, p(k_2)\, p(c_k)\, p(c_{k_1})\, p(c_{k_2})$.

E.4 Posterior for $\theta_{t,m}$

The posterior for $\theta_{t,m}$ is as follows:

$$\begin{aligned} &p(\theta_{t,m} \mid \boldsymbol{Y}_n, \sigma^2, \Pi) \propto p(\boldsymbol{Y}_n \mid \theta_{t,m}, \sigma^2, \Pi)\, p(\theta_{t,m}) \\ &\propto (2\pi\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2}\sum(Y_i - \theta_{t,m})^2\}(\frac{2\pi\sigma^2}{\kappa_0})^{-1/2} \exp\{-\frac{\kappa_0}{2\sigma^2}(\theta_{t,m} - \theta_0)^2\} \\ &\propto \exp\{-\frac{1}{2\sigma^2}[\sum(Y_i - \theta_{t,m})^2 + \kappa_0(\theta_{t,m} - \theta_0)^2]\} \end{aligned}$$

$$
\begin{aligned}
&\propto \exp\{-\frac{1}{2\sigma^2}[\sum(Y_i^2) - 2\theta_{t,m}\sum Y_i + n\theta_{t,m}^2 + \kappa_0\theta_{t,m}^2 - 2\kappa_0\theta_0\theta_{t,m} + \kappa_0\theta_0^2]\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}[(n+\kappa_0)\theta_{t,m}^2 - 2(\sum Y_i + \kappa_0\theta_0)\theta_{t,m} + (\sum(Y_i^2) + \kappa_0\theta_0^2)]\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}[a\theta_{t,m}^2 + 2b\theta_{t,m} + c]\} \\
&\text{where } a = n+\kappa_0; b = \sum Y_i + \kappa_0\theta_0; c = \sum(Y_i^2) + \kappa_0\theta_0^2 \\
&\propto \exp\{-\frac{1}{2\sigma^2}[a\theta_{t,m}^2 + 2b\theta_{t,m}]\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m}]\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2 - (\frac{b}{a})^2]\} \text{ (complete the square)} \\
&\propto \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2] + \frac{1}{2\sigma^2}(\frac{b^2}{a})\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2]\} \\
&\propto \exp\{-\frac{1}{2\sigma^2}a(\theta_{t,m} - \frac{b}{a})^2\} \\
&\propto \exp\{-\frac{1}{2(\frac{\sigma^2}{a})}(\theta_{t,m} - \frac{b}{a})^2\},
\end{aligned}
$$

so that

$$
\theta_{t,m} \mid \boldsymbol{Y}_n, \sigma^2, \Pi \sim \mathcal{N}(\frac{b}{a}, \frac{\sigma^2}{a}) = \mathcal{N}(\frac{\sum Y_i + \kappa_0\theta_0}{n+\kappa_0}, \frac{\sigma^2}{n+\kappa_0}).
$$

E.5 Posterior for σ^2

The posterior for σ^2 is computed as follows:

$$
\begin{aligned}
&p(\sigma^2 \mid \boldsymbol{Y}_n, \theta_{t,m}) \propto p(\boldsymbol{Y}_n \mid \theta_{t,m}, \sigma^2, \Pi)\, p(\sigma^2) \\
&\propto (2\pi\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2}\sum(Y_i - \theta_{t,m})^2\} \frac{(\frac{SS_0^2}{2})^{\frac{\nu_0}{2}}}{\Gamma(\frac{\nu_0}{2})} (\sigma^2)^{-\frac{\nu_0}{2}-1} \exp\{-\frac{SS_0^2}{2\sigma^2}\} \\
&\propto (\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2}\sum(Y_i - \theta_{t,m})^2\} (\sigma^2)^{-\frac{\nu_0}{2}-1} \exp\{-\frac{SS_0^2}{2\sigma^2}\} \\
&\propto (\sigma^2)^{-\frac{(n+\nu_0)}{2}-1} \exp\{-\frac{1}{2\sigma^2}[SS_0^2 + \sum(Y_i - \theta_{t,m})^2\} \\
&\propto (\sigma^2)^{-\frac{(n+\nu_0)}{2}-1} \exp\{-\frac{1}{\sigma^2}[\frac{SS_0^2}{2} + \frac{\sum(Y_i - \theta_{t,m})^2}{2}\} \\
&\text{Let } \nu_n = n + \nu_0 \text{ and } SS_n = SS_0^2 + \sum(Y_i - \theta_{t,m})^2,
\end{aligned}
$$

so that

$$\sigma^2 \mid \boldsymbol{Y}_n \sim IG(\frac{\nu_n}{2}, \frac{SS_n}{2}).$$

E.6 Posterior for Π

We may now report the posterior for the partition Π:

$$p(\Pi \mid \boldsymbol{Y}_n, \sigma^2) = p(\Pi) \cdot \prod_{m,t} \int p(\boldsymbol{Y}_n \mid \theta_{t,m}, \sigma^2, \Pi)\, p(\theta_{t,m}) d\theta_{t,m}$$

$$= p(\Pi) \cdot \prod_{m,t} \int (2\pi\sigma^2)^{-n/2} \exp\{-\frac{1}{2\sigma^2} \sum_{i,t,m} (Y_{i;t,m} - \theta_{t,m})^2\}$$

$$(\frac{2\pi\sigma^2}{\kappa_0})^{-1/2} \exp\{-\frac{\kappa_0}{2\sigma^2}(\theta_{t,m} - \theta_0)^2\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \int \exp\{-\frac{1}{2\sigma^2}[\sum_{i,t,m} (Y_{i;t,m} - \theta_{t,m})^2 + \kappa_0(\theta_{t,m} - \theta_0)^2]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \int \exp\{-\frac{1}{2\sigma^2}[\sum_{i,t,m} (Y_{i;t,m}^2)$$

$$-2\theta_{t,m} \sum_{i,t,m} Y_{i;t,m} + n\theta_{t,m}^2 + \kappa_0\theta_{t,m}^2 - 2\kappa_0\theta_0\theta_{t,m} + \kappa_0\theta_0^2]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \int \exp\{-\frac{1}{2\sigma^2}[(n + \kappa_0)\theta_{t,m}^2$$

$$-2(\sum_{i,t,m} Y_{i;t,m} + \kappa_0\theta_0)\theta_{t,m} + (\sum_{i,t,m} (Y_{i;t,m}^2) + \kappa_0\theta_0^2)]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \int \exp\{-\frac{1}{2\sigma^2}[a\theta_{t,m}^2 + 2b\theta_{t,m} + c]\} d\theta_{t,m}$$

$$\text{where } a = n_{mt} + \kappa_0; b = \sum_{i,t,m} Y_{i;t,m} + \kappa_0\theta_0; c = \sum_{i,t,m} (Y_{i;t,m}^2) + \kappa_0\theta_0^2$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \int \exp\{-\frac{1}{2\sigma^2}[a\theta_{t,m}^2 + 2b\theta_{t,m}]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \int \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m}]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \int \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2 - (\frac{b}{a})^2]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \int \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2] + \frac{1}{2\sigma^2}(\frac{b^2}{a})\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \exp\{\frac{1}{2\sigma^2}(\frac{b^2}{a})\} \int \exp\{-\frac{1}{2\sigma^2}a[\theta_{t,m}^2 + \frac{2b}{a}\theta_{t,m} + (\frac{b}{a})^2]\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \exp\{\frac{1}{2\sigma^2}(\frac{b^2}{a})\} \int \exp\{-\frac{1}{2\sigma^2}a(\theta_{t,m} - \frac{b}{a})^2\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \exp\{\frac{1}{2\sigma^2}(\frac{b^2}{a})\} \int \exp\{-\frac{1}{2(\frac{\sigma^2}{a})}(\theta_{t,m} - \frac{b}{a})^2\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \exp\{\frac{1}{2\sigma^2}(\frac{b^2}{a})\} (2\pi(\frac{\sigma^2}{a}))^{1/2}$$

$$\int (2\pi(\frac{\sigma^2}{a}))^{-1/2} \exp\{-\frac{1}{2(\frac{\sigma^2}{a})}(\theta_{t,m} - \frac{b}{a})^2\} d\theta_{t,m}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2} (\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t} \exp\{-\frac{1}{2\sigma^2}c\} \exp\{\frac{1}{2\sigma^2}(\frac{b^2}{a})\} (2\pi(\frac{\sigma^2}{a}))^{1/2}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2}(\frac{2\pi\sigma^2}{\kappa_0})^{-1/2} \cdot \prod_{m,t}(2\pi(\frac{\sigma^2}{a}))^{1/2} \exp\{-\frac{1}{2\sigma^2}[c - (\frac{b^2}{a})]\}$$

$$= p(\Pi) \cdot (2\pi\sigma^2)^{-n/2}(\frac{2\pi\sigma^2}{\kappa_0})^{-1/2}$$

$$\cdot \prod_{m,t}(2\pi(\frac{\sigma^2}{n_{mt} + \kappa_0}))^{1/2} \exp\{-\frac{1}{2\sigma^2}[\sum_{i,t,m}(Y_{i;t,m}^2) + \kappa_0\theta_0^2 - \frac{(\sum_{i,t,m} Y_i + \kappa_0\theta_0)^2}{n_{mt} + \kappa_0}]\}.$$

Appendix F Regression Model

In this section, we describe the details for the Regression model. We begin with some notation. Let n_{mt} denote the number of patients in subgroup m receiving treatment t. Let X_i, where $i = 1 \dots n_{mt}$, denote the set of biomarker readings for patient i in subgroup m receiving treatment t and Y_i be the corresponding response for that particular patient. Let $\boldsymbol{Y}_n$ denote the collection of all patient responses, all of whom are independent of one another. Similarly, let $\boldsymbol{X}_n$ denote the collection of all biomarker profiles. Let $\boldsymbol{\beta}_{t,m}$ be the linear regression coefficient vector for patients in subgroup m with treatment t and let $\boldsymbol{\beta}$ be the collection of all $\boldsymbol{\beta}_{t,m}$. We say that NB represents the number of biomarkers, and that $\mathcal{N}(a, b)$ represents the Gaussian distribution with mean a and variance b. Additionally, $IG(a, b)$ will represent the inverse Gamma distribution with mean b/a.

We have that,

$$Y_i = X_i^T \boldsymbol{\beta}_{t,m} + \epsilon_i, \tag{F.1}$$

where the vectors X_i and $\boldsymbol{\beta}_{t,m}$ are of dimension $NB \times 1$ and $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$. Furthermore,

$$p(Y_i|X_i, \boldsymbol{\beta}_{t,m}, \sigma) = \frac{1}{\sigma\sqrt{(2\pi)}} \exp\left(-\frac{(Y_i - X_i^T \boldsymbol{\beta}_{t,m})^T (Y_i - X_i^T \boldsymbol{\beta}_{t,m})}{2\sigma^2}\right). \tag{F.2}$$

F.1 Likelihood

From the computations above, the likelihood is:

$$p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{\beta}, \sigma^2) = \prod_{t=1}^{T} \prod_{m=1}^{M} \prod_{i \in S_m, z_i = t} p(Y_i|X_i, \boldsymbol{\beta}_{t,m}, \sigma^2),$$

or

$$\prod_{t=1}^{T} \prod_{m=1}^{M} \left(\frac{1}{\sigma\sqrt{(2\pi)}}\right)^{n_{mt}} \exp\left\{-\frac{(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T \boldsymbol{\beta}_{t,m})^T (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T \boldsymbol{\beta}_{t,m})}{2\sigma^2}\right\},$$

where $\mathbf{Y}_{t,m} = \{Y_i\}_{i \in S_m, z_i = t}$, the vector of all the patient responses for patients in subgroup m receiving treatment t and $\mathbf{X}_{t,m} = \{X_i\}_{i \in S_m, z_i = t}$, the matrix of patient biomarker values for patients in subgroup m receiving treatment t.

F.2 Priors

We now specify the priors $p(\boldsymbol{\beta}_{t,m})$ and $p(\sigma^2)$ where $p(\boldsymbol{\beta}_{t,m})$ takes a multivariate normal form and $p(\sigma^2)$ an inverse gamma form. We have that

$$p(\boldsymbol{\beta}_{t,m}) = \mathcal{N}(\mu_0, \Sigma_0) = \frac{1}{\sqrt{(2\pi)^{NB}\,|\Sigma_0|}}\, exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m} - \mu_0)^T\, \Sigma_0^{-1}\, (\boldsymbol{\beta}_{t,m} - \mu_0)\}, \quad \text{(F.3)}$$

and that

$$p(\sigma^2) = IG(a_0, b_0) = \frac{b_0^{a_0}}{\Gamma(a_0)}\, (\sigma^2)^{-a_0 - 1}\, exp\{-\frac{b_0}{\sigma^2}\}. \quad \text{(F.4)}$$

We use variables with a subscript 0 to indicate hyperparameters.

F.3 Joint Model

Packaging the likelihood and priors together, it follows that the joint model is:

$$p(\boldsymbol{Y}_n, \boldsymbol{\beta}, \sigma^2, \Pi | \boldsymbol{X}_n) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{\beta}, \sigma^2, \Pi)\, p(\boldsymbol{\beta}|\Pi)\, p(\sigma^2)\, p(\Pi|\boldsymbol{c})\, p(\boldsymbol{c}),$$

which is proportional to

$$\begin{aligned}
&\prod_{t=1}^{T} \prod_{m=1}^{M} \frac{1}{\sigma^{n_{mt}} \sqrt{(2\pi)^{n_{mt}}}} \exp\{-\frac{1}{2}(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\, \boldsymbol{\beta}_{t,m})^T\, (\sigma^2\, I)^{-1}\, (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\, \boldsymbol{\beta}_{t,m})\} \\
&\quad \cdot \frac{1}{\sqrt{(2\pi)^{NB}\,|\Sigma_0|}}\, \exp\{\frac{-1}{2}(\boldsymbol{\beta}_{t,m} - \mu_0)^T\, \Sigma_0^{-1}\, (\boldsymbol{\beta}_{t,m} - \mu_0)\} \\
&\quad \cdot \frac{b_0^{a_0}}{\Gamma(a_0)}\, (\sigma^2)^{-a_0 - 1}\, \exp\{\frac{-b_0}{\sigma^2}\} \cdot p(\boldsymbol{c}).
\end{aligned}$$

Then, we may simplify this to:

$$\prod_{t=1}^{T}\prod_{m=1}^{M}\frac{1}{\sigma^{n_{mt}}}\exp\{-\frac{1}{2}(\mathbf{Y}_{t,m}-\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m})^{T}(\sigma^{2}I)^{-1}(\mathbf{Y}_{t,m}-\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m})\}$$
$$\cdot\exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m}-\mu_{0})^{T}\Sigma_{0}^{-1}(\boldsymbol{\beta}_{t,m}-\mu_{0})\}\cdot(\sigma^{2})^{-a_{0}-1}\exp\{\frac{-b_{0}}{\sigma^{2}}\}\cdot p(\boldsymbol{c}).$$

In the above, $p(\boldsymbol{c}) = p(k)\,p(k_1)\,p(k_2)\,p(c_k)\,p(c_{k_1})\,p(c_{k_2})$. More details on the exact form of $p(\boldsymbol{c})$ are given in Appendix A. Note that,

$$(\mathbf{Y}_{t,m}-\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m})^{T}(\sigma^{2}I)^{-1}(\mathbf{Y}_{t,m}-\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m})+(\boldsymbol{\beta}_{t,m}-\mu_{0})^{T}\Sigma_{0}^{-1}(\boldsymbol{\beta}_{t,m}-\mu_{0})$$

$$=\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}-\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m}-\boldsymbol{\beta}_{t,m}^{T}\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}$$
$$-\boldsymbol{\beta}_{t,m}^{T}\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}\boldsymbol{\beta}_{t,m}+\boldsymbol{\beta}_{t,m}^{T}\Sigma_{0}^{-1}\boldsymbol{\beta}_{t,m}$$
$$-\boldsymbol{\beta}_{t,m}^{T}\Sigma_{0}^{-1}\mu_{0}-\mu_{0}^{T}\Sigma_{0}^{-1}\boldsymbol{\beta}_{t,m}+\mu_{0}^{T}\Sigma_{0}^{-1}\mu_{0}$$

$$=\boldsymbol{\beta}_{t,m}^{T}(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}+\Sigma_{0}^{-1})\boldsymbol{\beta}_{t,m}-(\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}+\mu_{0}^{T}\Sigma_{0}^{-1})\boldsymbol{\beta}_{t,m}$$
$$-\boldsymbol{\beta}_{t,m}^{T}(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}+\Sigma_{0}^{-1}\mu_{0})+\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}+\mu_{0}^{T}\Sigma_{0}^{-1}\mu_{0}$$

Now complete the square by adding and subtracting $\mu_n^T\Sigma_n^{-1}\mu_n$.

$$=\boldsymbol{\beta}_{t,m}^{T}(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}+\Sigma_{0}^{-1})\boldsymbol{\beta}_{t,m}-(\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}+\mu_{0}^{T}\Sigma_{0}^{-1})\boldsymbol{\beta}_{t,m}$$
$$-\boldsymbol{\beta}_{t,m}^{T}(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}+\Sigma_{0}^{-1}\mu_{0})+\mu_{n}^{T}\Sigma_{n}^{-1}\mu_{n}-$$
$$\mu_{n}^{T}\Sigma_{n}^{-1}\mu_{n}+\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}+\mu_{0}^{T}\Sigma_{0}^{-1}\mu_{0}$$

$$=(\boldsymbol{\beta}_{t,m}-\mu_{n})^{T}\Sigma_{n}^{-1}(\boldsymbol{\beta}_{t,m}-\mu_{n})+\mathbf{Y}_{t,m}^{T}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}-\mu_{n}^{T}\Sigma_{n}^{-1}\mu_{n}+\mu_{0}^{T}\Sigma_{0}^{-1}\mu_{0}$$

where

$$\mu_{n}=(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{X}_{t,m}^{T}+\Sigma_{0}^{-1})^{-1}(\mathbf{X}_{t,m}(\sigma^{2}I)^{-1}\mathbf{Y}_{t,m}+\Sigma_{0}^{-1}\mu_{0})$$

and

$$\Sigma_n = (\mathbf{X}_{t,m}\,(\sigma^2\,I)^{-1}\,\mathbf{X}_{t,m}^T + \Sigma_0^{-1})^{-1}.$$

Therefore, we can write our joint model in the following way:

$$\begin{aligned} p(\boldsymbol{Y}_n, \boldsymbol{\beta}, \sigma^2, \Pi | \boldsymbol{X}_n) &\propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{\beta}, \sigma^2, \Pi)\, p(\boldsymbol{\beta}|\Pi)\, p(\sigma^2)\, p(\Pi|\boldsymbol{c})\, p(\boldsymbol{c}) \\ &\propto \prod_{t=1}^{T}\prod_{m=1}^{M} \sigma^{-n_{mt}}\, \exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m} - \mu_n)^T\, \Sigma_n^{-1}\, (\boldsymbol{\beta}_{t,m} - \mu_n)\} \\ &\quad \cdot \exp\{-\frac{1}{2}(\mathbf{Y}_{t,m}^T\,(\sigma^2\,I)^{-1}\,\mathbf{Y}_{t,m} - \mu_n^T\,\Sigma_n^{-1}\,\mu_n + \mu_0^T\,\Sigma_0^{-1}\,\mu_0)\} \\ &\quad \cdot (\sigma^2)^{-a_0-1}\, \exp\{\frac{-b_0}{\sigma^2}\} \cdot p(\boldsymbol{c}) \end{aligned}$$

F.4 Posterior for $\beta_{t,m}$

We may now write the posterior for $\beta_{t,m}$ as

$$\begin{aligned} p(\boldsymbol{\beta}_{t,m} | \boldsymbol{Y}_n, \boldsymbol{X}_n, \Pi) &\propto \exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m} - \mu_n)^T\, \Sigma_n^{-1}\, (\boldsymbol{\beta}_{t,m} - \mu_n)\} \\ &\propto \mathcal{N}(\mu_n, \Sigma_n), \end{aligned}$$

where $\mathcal{N}(\mu_n, \Sigma_n)$ denotes a multivariate normal pdf with mean vector μ_n and covariance matrix Σ_n.

F.5 Posterior for σ^2

We may now write the posterior for σ^2:

$$\begin{aligned} &p(\sigma^2 | \boldsymbol{Y}_n, \boldsymbol{X}_n) \\ &\propto (\sigma^2)^{-a_0-1}\, \exp\{\frac{-b_0}{\sigma^2}\} \\ &\cdot \prod_{t=1}^{T}\prod_{m=1}^{M} \frac{1}{\sigma^{n_{mt}}\sqrt{(2\pi)^{n_{mt}}}} \exp\{-\frac{1}{2\sigma^2}(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\,\boldsymbol{\beta}_{t,m})^T(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\,\boldsymbol{\beta}_{t,m})\} \\ &\propto (\sigma^2)^{-(a_0 + \frac{1}{2}\sum_{m,t} n_{mt})-1} \\ &\cdot \exp\{-\frac{1}{\sigma^2}(b_0 + \frac{1}{2}\sum_{m,t}[(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\,\boldsymbol{\beta}_{t,m})^T(\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T\,\boldsymbol{\beta}_{t,m})]\}, \end{aligned}$$

where

$$a_n = a_0 + \frac{1}{2}\sum_{m,t} n_{mt},$$

$$b_n = b_0 + \frac{1}{2}\sum_{m,t} (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T \boldsymbol{\beta}_{t,m})^T (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}^T \boldsymbol{\beta}_{t,m}),$$

and $IG(a_n, b_n)$ denotes an inverse-gamma pdf with mean a_n and variance b_n.

F.6 Posterior for Π

Finally, we report the posterior distribution on the partition Π:

$$\begin{aligned}
&p(\Pi|\boldsymbol{Y}_n, \boldsymbol{X}_n, \sigma^2) \\
&= p(\Pi) \cdot \int p(\boldsymbol{Y}_n \mid \beta, \sigma, \Pi)\, p(\beta|\Pi) d\beta \\
&= p(\Pi) \cdot \prod_{t=1}^{T}\prod_{m=1}^{M} \int \sigma^{-n_{mt}} (2\pi)^{-n_{mt}/2} \\
&\exp\{-\frac{1}{2\sigma^2} (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}\beta_{t,m})^T (\mathbf{Y}_{t,m} - \mathbf{X}_{t,m}\beta_{t,m})\} \\
&\cdot \frac{1}{\sqrt{(2\pi)^{NB}|\Sigma_0|}} \exp\{-\frac{1}{2}(\beta_{t,m} - \mu_0)^T \Sigma_0^{-1} (\beta_{t,m} - \mu_0)\} d\beta_{t,m} \\
&= p(\Pi) \cdot \prod_{t=1}^{T}\prod_{m=1}^{M} \frac{\sigma^{-n_{mt}} (2\pi)^{-n_{mt}/2}}{\sqrt{(2\pi)^{NB}|\Sigma_0|}} \cdot \int \exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m} - \mu_n)^T \Sigma_n^{-1} (\boldsymbol{\beta}_{t,m} - \mu_n)\} \\
&\cdot \exp\{-\frac{1}{2}\mathbf{Y}_{t,m}^T (\sigma^2 I)^{-1} \mathbf{Y}_{t,m}\} \cdot \exp\{\frac{1}{2}\mu_n^T \Sigma_n^{-1} \mu_n\} \cdot \exp\{-\frac{1}{2}\mu_0^T \Sigma_0^{-1} \mu_0\} d\boldsymbol{\beta}_{t,m} \\
&= p(\Pi) \cdot \prod_{t=1}^{T}\prod_{m=1}^{M} \frac{\sigma^{-n_{mt}} (2\pi)^{-n_{mt}/2}}{\sqrt{(2\pi)^{NB}|\Sigma_0|}} \\
&\cdot \exp\{-\frac{1}{2}\mathbf{Y}_{t,m}^T (\sigma^2 I)^{-1} \mathbf{Y}_{t,m}\} \cdot \exp\{\frac{1}{2}\mu_n^T \Sigma_n^{-1} \mu_n\} \\
&\cdot \exp\{-\frac{1}{2}\mu_0^T \Sigma_0^{-1} \mu_0\} \cdot \int \exp\{-\frac{1}{2}(\boldsymbol{\beta}_{t,m} - \mu_n)^T \Sigma_n^{-1} (\boldsymbol{\beta}_{t,m} - \mu_n)\} d\boldsymbol{\beta}_{t,m} \\
&= p(\Pi) \cdot \prod_{t=1}^{T}\prod_{m=1}^{M} \frac{\sigma^{-n_{mt}} (2\pi)^{-n_{mt}/2}}{\sqrt{(2\pi)^{NB}|\Sigma_0|}} \cdot \sqrt{(2\pi)^{NB}|\Sigma_n|} \\
&\cdot \exp\{-\frac{1}{2}\mathbf{Y}_{t,m}^T (\sigma^2 I)^{-1} \mathbf{Y}_{t,m}\} \cdot \exp\{\frac{1}{2}\mu_n^T \Sigma_n^{-1} \mu_n\} \\
&\cdot \exp\{-\frac{1}{2}\mu_0^T \Sigma_0^{-1} \mu_0\}
\end{aligned}$$

$$= p(\Pi) \cdot \prod_{t=1}^{T} \prod_{m=1}^{M} \sigma^{-n_{mt}} \, (2\pi)^{-n_{mt}/2} \cdot \sqrt{(\frac{|\Sigma_n|}{|\Sigma_0|})} \cdot \exp\{-\frac{1}{2} \mathbf{Y}_{t,m}^T \, (\sigma^2 \, I)^{-1} \, \mathbf{Y}_{t,m}\}$$
$$\cdot \exp\{\frac{1}{2} \mu_n^T \, \Sigma_n^{-1} \, \mu_n\} \cdot \exp\{-\frac{1}{2} \mu_0^T \, \Sigma_0^{-1} \, \mu_0\}$$

Appendix G MCMC

In this section, we describe a Metropolis-Hasting algorithm to update the partition in each iteration. The algorithm has three steps, which we will describe in what follows. As a reminder, we use the letter k to denote the index of the biomarker for the first split, and k_1 and k_2 denote the indices of the biomarkers for the second splits. The variables c_k^s, $c_{k_1}^s$, and $c_{k_2}^s$ denote the locations of the splits. The superscript s represents the s^{th} iteration; we will drop the superscript when it is clear from context what we mean.

G.1 Step 1: Keep k, k_1, k_2 fixed, update c_k, c_{k_1}, c_{k_2}

In the first step, we fix the biomarkers to split on, and update the locations of the splits. Denote which biomarkers are split upon in the current partition and the location of those respective splits by $\boldsymbol{c} = (k^s, k_1^s, k_2^s, c_k^s, c_{k_1}^s, c_{k_2}^s)$ in iteration s. We propose candidate splits with $\boldsymbol{c}^* = (k^s, k_1^s, k_2^s, c_k^*, c_{k_1}^*, c_{k_2}^*)$ as follows.

G.1.1 Discrete Biomarkers

When the biomarkers are not all continuous, we use the prior densities as proposals.

G.1.2 Continuous Biomarkers

When all of the variables (biomarkers) are continuous, we have that $c_k^s, c_{k_1}^s, c_{k_2}^s \in [-1, 1]$. Thus, we use a normal proposal density on the transformed scale, i.e.,

$$\eta_k^s = \log \frac{1 + c_k^s}{1 - c_k^s} \in (-\infty, \infty).$$

We take c_k^s, $c_{k_1}^s$, and $c_{k_2}^s$ and transform them into η_k^s, $\eta_{k_1}^s$, and $\eta_{k_2}^s$ respectively to occupy the real line. Then, we generate η_k^*, $\eta_{k_1}^*$, and $\eta_{k_2}^*$ to be random normal variables with means η_k^s, $\eta_{k_1}^s$, and $\eta_{k_2}^s$ respectively and variance σ^2. Finally to obtain c_k^*, $c_{k_1}^*$, and $c_{k_2}^*$ we must transform back to the original ranges that c_k^s, $c_{k_1}^s$, and $c_{k_2}^s$ were in. Thus, we

k	$c_k \in [-1,1]$	$\eta_k = \log\frac{1+c_k}{1-c_k} \in (-\infty,\infty)$	$\eta_k^* \sim \mathcal{N}(\eta_k,\sigma^2)$	$c_k^* = \frac{\exp(\eta_k^*)-1}{\exp(\eta_k^*)+1} \in [-1,1]$
$k_1 \neq k$	$c_{k_1} \in [-1,1]$	$\eta_{k_1} = \log\frac{1+c_{k_1}}{1-c_{k_1}} \in (-\infty,\infty)$	$\eta_{k_1}^* \sim \mathcal{N}(\eta_{k_1},\sigma^2)$	$c_{k_1}^* = \frac{\exp(\eta_{k_1}^*)-1}{\exp(\eta_{k_1}^*)+1} \in [-1,1]$
$k_2 \neq k$	$c_{k_2} \in [-1,1]$	$\eta_{k_2} = \log\frac{1+c_{k_2}}{1-c_{k_2}} \in (-\infty,\infty)$	$\eta_{k_2}^* \sim \mathcal{N}(\eta_{k_2},\sigma^2)$	$c_{k_2}^* = \frac{\exp(\eta_{k_2}^*)-1}{\exp(\eta_{k_2}^*)+1} \in [-1,1]$
$k_1 = k$	$c_{k_1} \in [-1,c_k]$	$\eta_{k_1} = \log\frac{1+c_{k_1}}{c_k-c_{k_1}} \in (-\infty,\infty)$	$\eta_{k_1}^* \sim \mathcal{N}(\eta_{k_1},\sigma^2)$	$c_{k_1}^* = \frac{c_k^*\,\exp(\eta_{k_1}^*)-1}{\exp(\eta_{k_1}^*)+1} \in [-1,c_k]$
$k_2 = k$	$c_{k_2} \in [c_k,1]$	$\eta_{k_2} = \log\frac{-c_k+c_{k_2}}{1-c_{k_2}} \in (-\infty,\infty)$	$\eta_{k_2}^* \sim \mathcal{N}(\eta_{k_2},\sigma^2)$	$c_{k_2}^* = \frac{\exp(\eta_{k_2}^*)+c_k^*}{\exp(\eta_{k_2}^*)+1} \in [c_k,1]$

Table 2: The continuous biomarker MCMC sampling transformations.

can summarize this transformation as follows:

$$c_k^s \to \eta_k^s \to \eta_k^* \sim \mathcal{N}(\eta_k^s,\sigma^2) \to c_k^*. \tag{G.1}$$

With a new c^*, we have a new partition Π. We summarize all the transformations in Table 2.

G.1.3 Posterior Ratio

Recall that the joint hierarchical model is

$$p(\boldsymbol{Y}_n,\Theta,\boldsymbol{\Pi} \mid \boldsymbol{X}_n,\boldsymbol{Z}_n) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n,\boldsymbol{Z}_n,\Theta,\boldsymbol{\Pi})\,p(\Theta \mid \boldsymbol{\Pi})\,p(\boldsymbol{\Pi} \mid \boldsymbol{c})p(\boldsymbol{c}).$$

Thus, in a similar manner, we may write

$$p(\boldsymbol{Y}_n,\Theta,\boldsymbol{\Pi}^* \mid \boldsymbol{X}_n,\boldsymbol{Z}_n) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n,\boldsymbol{Z}_n,\Theta,\boldsymbol{\Pi}^*)\,p(\Theta \mid \boldsymbol{\Pi}^*)\,p(\boldsymbol{\Pi}^* \mid \boldsymbol{c}^*)p(\boldsymbol{c}^*)$$

Then, the MCMC posterior ratio is:

$$\frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n,\boldsymbol{Z}_n,\Theta,\boldsymbol{\Pi}^*)\,p(\Theta \mid \boldsymbol{\Pi}^*)\,p(\boldsymbol{\Pi}^* \mid \boldsymbol{c}^*)p(\boldsymbol{c}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n,\boldsymbol{Z}_n,\Theta,\boldsymbol{\Pi})\,p(\Theta \mid \boldsymbol{\Pi})\,p(\boldsymbol{\Pi} \mid \boldsymbol{c})p(\boldsymbol{c})}.$$

G.1.4 Proposal Ratio

Let us now consider the MCMC proposal ratio. In the discrete case, it is the ratio of the priors, and is simple. We state the continuous case here in more detail: Recall $\eta_k = log\frac{1+c_k}{1-c_k}$. Therefore,

$$\frac{q(c_k \mid c_k^*)}{q(c_k^* \mid c_k)} = \frac{q(\eta_k \mid \eta_k^*)}{q(\eta_k^* \mid \eta_k)} \cdot \frac{d\eta_k/dc_k}{d\eta_k^*/dc_k^*},$$

which is

$$1 \cdot \frac{(1+c_k^*)(1-c_k^*)}{(1+c_k)(1-c_k)} = \frac{(1+c_k^*)(1-c_k^*)}{(1+c_k)(1-c_k)}.$$

If $k_1 \neq k$, then recall that $\eta_{k_1} = log\frac{1+c_{k_1}}{1-c_{k_1}}$. Therefore,

$$\frac{q(c_{k_1} \mid c_{k_1}^*)}{q(c_{k_1}^* \mid c_{k_1})} = \frac{q(\eta_{k_1} \mid \eta_{k_1}^*)}{q(\eta_{k_1}^* \mid \eta_{k_1})} \cdot \frac{d\eta_{k_1}/dc_{k_1}}{d\eta_{k_1}^*/dc_{k_1}^*},$$

which is

$$1 \cdot \frac{(1+c_{k_1}^*)(1-c_{k_1}^*)}{(1+c_{k_1})(1-c_{k_1})} = \frac{(1+c_{k_1}^*)(1-c_{k_1}^*)}{(1+c_{k_1})(1-c_{k_1})}.$$

If $k_2 \neq k$, then recall that $\eta_{k_2} = log\frac{1+c_{k_2}}{1-c_{k_2}}$. Therefore,

$$\frac{q(c_{k_2} \mid c_{k_2}^*)}{q(c_{k_2}^* \mid c_{k_2})} = \frac{q(\eta_{k_2} \mid \eta_{k_2}^*)}{q(\eta_{k_2}^* \mid \eta_{k_2})} \cdot \frac{d\eta_{k_2}/dc_{k_2}}{d\eta_{k_2}^*/dc_{k_2}^*},$$

which is

$$1 \cdot \frac{(1+c_{k_2}^*)(1-c_{k_2}^*)}{(1+c_{k_2})(1-c_{k_2})} = \frac{(1+c_{k_2}^*)(1-c_{k_2}^*)}{(1+c_{k_2})(1-c_{k_2})}.$$

If $k_1 = k$, then recall that $\eta_{k_1} = log\frac{1+c_{k_1}}{c_k-c_{k_1}}$. Therefore,

$$\frac{q(c_{k_1} \mid c_{k_1}^*)}{q(c_{k_1}^* \mid c_{k_1})} = \frac{q(\eta_{k_1} \mid \eta_{k_1}^*)}{q(\eta_{k_1}^* \mid \eta_{k_1})} \cdot \frac{d\eta_{k_1}/dc_{k_1}}{d\eta_{k_1}^*/dc_{k_1}^*},$$

which is

$$\frac{1+c_k}{(1+c_{k_1})(c_k-c_{k_1})} \cdot \frac{(1+c_{k_1}^*)(c_k^*-c_{k_1}^*)}{1+c_k^*}.$$

If $k_2 = k$, then recall that $\eta_{k_2} = \log \frac{-c_k + c_{k_2}}{1 - c_{k_2}}$. Therefore,

$$\frac{q(c_{k_2} \mid c^*_{k_2})}{q(c^*_{k_2} \mid c_{k_2})} = \frac{q(\eta_{k_2} \mid \eta^*_{k_2})}{q(\eta^*_{k_2} \mid \eta_{k_2})} \cdot \frac{d\eta_{k_2}/dc_{k_2}}{d\eta^*_{k_2}/dc^*_{k_2}},$$

which is

$$\frac{1 - c_k}{(-c_k + c_{k_2})(1 - c_{k_2})} \cdot \frac{(-c^*_k + c^*_{k_2})(1 - c^*_{k_2})}{1 - c^*_k}.$$

G.1.5 Acceptance Ratio

The acceptance ratio is the product of the posterior ratio and the proposal ratio. Let r be the acceptance ratio. Then,

$$r = \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)\, p(\Theta \mid \boldsymbol{\Pi}^*)\, p(\boldsymbol{\Pi}^* \mid \boldsymbol{c}^*)\, p(\boldsymbol{c}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})\, p(\Theta \mid \boldsymbol{\Pi})\, p(\boldsymbol{\Pi} \mid \boldsymbol{c})\, p(\boldsymbol{c})} \cdot \frac{q(\boldsymbol{c} \mid \boldsymbol{c}^*)}{q(\boldsymbol{c}^* \mid \boldsymbol{c})}.$$

Note that $p(\boldsymbol{\Pi} \mid \boldsymbol{c}) = 1$ since if we know which biomarkers we split on and where along them we split we explicitly know the partition. Thus, we may write

$$\begin{aligned} r = {} & \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})} \\ & \cdot \frac{p(\Theta \mid \boldsymbol{\Pi}^*)\, p(k^*)\, p(k^*_1 \mid k^*)\, p(k^*_2 \mid k^*)\, p(c^*_k)\, p(c^*_{k_1} \mid k^*, c^*_k)\, p(c^*_{k_2} \mid k^*, c^*_k)}{p(\Theta \mid \boldsymbol{\Pi})\, p(k)\, p(k_1 \mid k)\, p(k_2 \mid k)\, p(c_k)\, p(c_{k_1} \mid k, c_k)\, p(c_{k_2} \mid k, c_k)} \\ & \cdot \frac{q(\boldsymbol{c} \mid \boldsymbol{c}^*)}{q(\boldsymbol{c}^* \mid \boldsymbol{c})}. \end{aligned}$$

We can further transform this expression into

$$\begin{aligned} r = {} & \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})} \\ & \cdot \frac{p(\Theta \mid \boldsymbol{\Pi}^*)\, p(k)\, p(k_1 \mid k)\, p(k_2 \mid k)\, p(c^*_k)\, p(c^*_{k_1} \mid k, c^*_k)\, p(c^*_{k_2} \mid k, c^*_k)}{p(\Theta \mid \boldsymbol{\Pi})\, p(k)\, p(k_1 \mid k)\, p(k_2 \mid k)\, p(c_k)\, p(c_{k_1} \mid k, c_k)\, p(c_{k_2} \mid k, c_k)} \cdot \frac{q(\boldsymbol{c} \mid \boldsymbol{c}^*)}{q(\boldsymbol{c}^* \mid \boldsymbol{c})}, \end{aligned}$$

since k, k_1, k_2 are fixed. Then, we have that

$$r = \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)\, p(\Theta \mid \boldsymbol{\Pi}^*)\, p(c_k^*)\, p(c_{k_1}^* \mid k, c_k^*)\, p(c_{k_2}^* \mid k, c_k^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})\, p(\Theta \mid \boldsymbol{\Pi})\, p(c_k)\, p(c_{k_1} \mid k, c_k)\, p(c_{k_2} \mid k, c_k)} \cdot \frac{q(\boldsymbol{c} \mid \boldsymbol{c}^*)}{q(\boldsymbol{c}^* \mid \boldsymbol{c})}.$$

G.1.6 Storing Values

We accept and store $\boldsymbol{c}^* = (k, k_1, k_2, c_k^*, c_{k_1}^*, c_{k_2}^*)$ with probability $\min(r, 1)$. If $\boldsymbol{c}^*$ is rejected, we instead store $\boldsymbol{c} = (k, k_1, k_2, c_k, c_{k_1}, c_{k_2})$.

G.2 Step 2: Update $k, k_1, k_2, c_k, c_{k_1}, c_{k_2}$

In this step, we update both the biomarker indices and the location of the splits.

G.2.1 New Biomarker indices

We uniformly sample new k^*, k_1^*, k_2^* values from the set of all biomarkers. We then propose a new set of biomarkers and split locations as $\boldsymbol{c}_* = (k^*, k_1^*, k_2^*, c_{k^*}, c_{k_1^*}, c_{k_2^*})$ using the priors (all of which are uniform) over the support of the relevant biomarkers.

G.2.2 Posterior Ratio

The posterior ratio in Step 2 is found exactly the same way as in Step 1.

G.2.3 Proposal Ratio

Let the proposal ratio in Step 2 be the ratio of the prior on our partition $\boldsymbol{\Pi}$ denoted $p(\boldsymbol{\Pi})$ to the prior on our partition $\boldsymbol{\Pi}^*$ denoted $p(\boldsymbol{\Pi}^*)$. This simplification occurs because all values are drawn uniformly from the priors.

G.2.4 Acceptance Ratio

Let r be the acceptance ratio. Then,

$$r = \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)\, p(\Theta \mid \boldsymbol{\Pi}^*)\, p(\boldsymbol{\Pi}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})\, p(\Theta \mid \boldsymbol{\Pi})\, p(\boldsymbol{\Pi})} \cdot \frac{q(\boldsymbol{\Pi} \mid \boldsymbol{\Pi}^*)}{q(\boldsymbol{\Pi}^* \mid \boldsymbol{\Pi})}.$$

We may write:

$$r = \frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)\, p(\Theta \mid \boldsymbol{\Pi}^*)\, p(\boldsymbol{\Pi}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})\, p(\Theta \mid \boldsymbol{\Pi})\, p(\boldsymbol{\Pi})} \cdot \frac{p(\boldsymbol{\Pi})}{p(\boldsymbol{\Pi}^*)},$$

which is

$$\frac{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi}^*)\, p(\Theta \mid \boldsymbol{\Pi}^*)}{p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \boldsymbol{\Pi})\, p(\Theta \mid \boldsymbol{\Pi})}.$$

G.2.5 Storing Values

We accept $\boldsymbol{c}_* = (k^*, k_1^*, k_2^*, c_{k^*}, c_{k_1^*}, c_{k_2^*})$ with probability $\min(r, 1)$. Otherwise, we keep the values stored in Step 1.

G.3 Step 3: Update model parameters

In this final step, we update the posterior Θ parameters for each sampling model. The details of this are found in Section 2.2.

Appendix H Tables of Results

H.1 Scenario 1

Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.961	0.697	0.612	0.889	0.588	0.464	0.65	0.457	0.047
	TNR	0.896	0.846	0.973	0.904	0.901	0.996	0.938	0.944	1
	SFE	0	0.018	0	0	0.008	0	0	0.002	0
	SUB	3.506	3.221	2.934	3.465	3.378	3.895	3.491	3.518	3.755
	ALL	1.88	1.803	1.923	1.777	1.81	1.419	1.807	1.762	1.715
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.985	0.71	0.654	0.965	0.6	0.558	0.802	0.468	0.265
	TNR	0.903	0.855	0.91	0.905	0.908	0.949	0.925	0.949	0.999
	SFE	0.002	0.012	0	0	0.004	0	0	0.001	0
	SUB	3.485	3.154	3.543	3.453	3.28	3.581	3.484	3.537	3.622
	ALL	1.837	1.731	2.5	1.776	1.824	1.96	1.811	1.846	2.111
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.982	0.715	0.785	0.981	0.604	0.316	0.832	0.471	0.048
	TNR	0.92	0.86	0.997	0.924	0.913	1	0.943	0.953	1
	SFE	0	0.011	0	0	0.004	0	0	0.001	0
	SUB	3.449	3.13	3.303	3.503	3.333	3.368	3.545	3.457	3.55
	ALL	1.779	1.813	1.835	1.809	1.782	1.578	1.82	1.857	1.405
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.994	0.705	0.936	0.993	0.588	0.923	0.883	0.447	0.875
	TNR	0.929	0.871	0.891	0.929	0.923	0.948	0.942	0.961	0.954
	SFE	0	0.008	0.001	0	0.002	0	0	0	0
	SUB	3.472	3.176	3.607	3.535	3.378	3.774	3.49	3.545	3.736
	ALL	1.74	1.76	0.96	1.83	1.826	1.861	1.785	1.848	1.962

Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.995	0.717	0.98	0.984	0.598	0.808	0.849	0.454	0.169
	TNR	0.939	0.867	1	0.939	0.925	1	0.949	0.967	1
	SFE	0.001	0.004	0	0	0.001	0	0	0	0
	SUB	3.512	3.074	4.096	3.566	3.301	3.669	3.557	3.478	4.337
	ALL	1.881	1.831	1.289	1.812	1.82	2.293	1.826	1.82	2.448
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.999	0.724	0.962	0.989	0.608	0.923	0.958	0.464	0.836
	TNR	0.934	0.878	1	0.934	0.933	1	0.938	0.971	1
	SFE	0	0.003	0	0	0.001	0	0	0	0
	SUB	3.42	3.097	4.188	3.567	3.281	3.657	3.473	3.483	2.766
	ALL	1.841	1.653	1.522	1.873	1.762	2.227	1.833	1.775	1.267
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.998	0.726	1	0.998	0.609	1	0.928	0.467	1
	TNR	0.935	0.868	0.943	0.935	0.922	0.952	0.943	0.961	0.978
	SFE	0	0.005	0	0	0.001	0	0	0	0
	SUB	3.466	3.154	3.875	3.46	3.261	4.976	3.453	3.456	3.847
	ALL	1.858	1.679	1.366	1.886	1.823	1.968	1.907	1.738	1.548
Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.999	0.74	0.99	0.999	0.627	0.961	0.979	0.486	0.907
	TNR	0.929	0.869	0.958	0.929	0.926	0.983	0.933	0.966	0.999
	SFE	0	0.004	0	0	0.002	0	0	0	0
	SUB	3.442	3.086	3.255	3.315	3.109	3.891	3.271	3.266	3.685
	ALL	1.926	1.765	2.813	1.811	1.788	1.891	1.735	1.752	4.516

Scenario 1		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.999	0.733	1	0.999	0.614	1	0.979	0.468	1
	TNR	0.937	0.884	0.889	0.937	0.94	0.949	0.937	0.976	0.996
	SFE	0	0.002	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 3: Scenario 1, $\delta = 0.5$

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.945	0.564	0.518	0.863	0.445	0.245	0.602	0.318	0
	TNR	0.925	0.918	0.989	0.936	0.952	1	0.966	0.974	1
	SFE	0	0.006	0	0	0.002	0	0	0	0
	SUB	3.625	3.404	3.424	3.629	3.552	3.746	3.651	3.676	3.739
	ALL	1.807	1.807	2.05	1.749	1.752	1.332	1.776	1.895	2.091

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.977	0.588	0.573	0.948	0.469	0.435	0.73	0.339	0.018
	TNR	0.939	0.922	0.938	0.939	0.955	0.983	0.956	0.978	1
	SFE	0.001	0.003	0	0	0.001	0	0	0	0
	SUB	3.646	3.292	3.778	3.613	3.507	3.583	3.633	3.617	3.581
	ALL	1.8	1.841	1.799	1.768	1.833	2.392	1.806	1.839	2.247

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.973	0.602	0.512	0.953	0.482	0.118	0.81	0.349	0.015
	TNR	0.949	0.921	1	0.953	0.955	1	0.965	0.979	1
	SFE	0	0.003	0	0	0.001	0	0	0	0
	SUB	3.588	3.291	3.664	3.607	3.444	2.993	3.604	3.597	3.24
	ALL	1.755	1.808	1.793	1.791	1.781	1.15	1.771	1.917	1.185

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.983	0.593	0.926	0.983	0.466	0.889	0.835	0.326	0.843
	TNR	0.957	0.93	0.948	0.958	0.962	0.953	0.968	0.983	0.957
	SFE	0	0.002	0	0	0	0	0	0	0
	SUB	3.591	3.393	3.453	3.618	3.529	4.135	3.632	3.676	3.391
	ALL	1.855	1.793	1.523	1.742	1.777	1.72	1.768	1.783	1.696

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.986	0.611	0.915	0.975	0.481	0.568	0.832	0.336	0.016
	TNR	0.961	0.929	1	0.962	0.966	1	0.97	0.987	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.628	3.222	4.019	3.597	3.473	4.374	3.616	3.604	3.712
	ALL	1.854	1.868	2.074	1.845	1.801	1.418	1.851	1.863	1.532

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.991	0.625	0.929	0.981	0.496	0.878	0.941	0.351	0.64
	TNR	0.961	0.935	1	0.961	0.969	1	0.966	0.988	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.51	3.397	3.348	3.541	3.458	3.186	3.607	3.603	3.408
	ALL	1.699	1.884	2.194	1.814	1.78	0.663	1.776	1.682	2.059

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.994	0.631	1	0.994	0.504	1	0.894	0.36	0.977
	TNR	0.965	0.921	0.95	0.965	0.957	0.967	0.971	0.981	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.432	3.246	2.874	3.605	3.396	3.339	3.615	3.593	4.671
	ALL	1.809	1.852	1.215	1.743	1.846	1.522	1.827	1.835	2.102

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.995	0.656	0.964	0.995	0.53	0.922	0.955	0.385	0.864
	TNR	0.96	0.923	0.982	0.96	0.961	0.998	0.961	0.984	1
	SFE	0	0.002	0	0	0.001	0	0	0	0
	SUB	3.692	3.396	1.792	3.613	3.418	3.761	3.508	3.391	4.315
	ALL	2.032	1.84	3.848	1.94	1.724	1.57	1.711	1.72	2.385

Scenario 1		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.995	0.646	1	0.995	0.515	1	0.975	0.366	0.993
	TNR	0.964	0.936	0.942	0.964	0.971	0.99	0.964	0.99	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 4: Scenario 1, $\delta = 0.7$

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.856	0.348	0.266	0.779	0.244	0.001	0.501	0.151	0
	TNR	0.963	0.973	1	0.971	0.985	1	0.986	0.993	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.75	3.564	3.348	3.736	3.7	3.584	3.753	3.741	3.903
	ALL	1.794	1.81	1.494	1.798	1.846	1.799	1.848	1.868	2.234

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.954	0.388	0.356	0.905	0.278	0.076	0.635	0.174	0
	TNR	0.971	0.976	0.992	0.972	0.988	1	0.983	0.996	1
	SFE	0.001	0	0	0	0	0	0	0	0
	SUB	3.651	3.586	4.008	3.692	3.654	3.769	3.669	3.682	3.61
	ALL	1.74	1.792	2.742	1.804	1.773	2.443	1.775	1.814	1.564

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.953	0.416	0.142	0.914	0.3	0.019	0.752	0.189	0
	TNR	0.978	0.974	1	0.979	0.988	1	0.987	0.996	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.704	3.478	3.399	3.65	3.567	3.25	3.738	3.662	3.76
	ALL	1.817	1.823	2.452	1.88	1.821	1.369	1.803	1.842	2.112

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.966	0.407	0.879	0.956	0.284	0.845	0.717	0.169	0.802
	TNR	0.986	0.976	0.953	0.986	0.988	0.958	0.991	0.996	0.979
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.724	3.649	4.18	3.743	3.713	3.659	3.745	3.755	3.451
	ALL	1.719	1.683	1.841	1.835	1.77	1.406	1.734	1.806	2.718

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.974	0.432	0.614	0.939	0.303	0.029	0.774	0.18	0
	TNR	0.987	0.98	1	0.987	0.992	1	0.993	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.741	3.625	3.749	3.724	3.595	3.935	3.73	3.692	
	ALL	1.772	1.905	1.157	1.746	1.867	1.882	1.766	1.767	1.696

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.98	0.455	0.859	0.972	0.325	0.709	0.902	0.198	0.185
	TNR	0.982	0.98	1	0.983	0.992	1	0.984	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.712	3.571	2.956	3.656	3.583	3.093	3.682	3.729	3.758
	ALL	1.882	1.849	1.308	1.756	1.793	0.827	1.834	1.767	2.492

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.981	0.473	1	0.973	0.343	0.98	0.845	0.214	0.842
	TNR	0.987	0.969	0.972	0.988	0.986	1	0.991	0.994	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.673	3.514	4.276	3.684	3.666	4.546	3.746	3.638	
	ALL	1.792	1.863	1.933	1.668	2.041	1.39	1.705	1.79	1.249

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.986	0.509	0.908	0.986	0.378	0.864	0.937	0.245	0.781
	TNR	0.985	0.971	0.999	0.985	0.987	1	0.985	0.995	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.716	3.559	3.83	3.689	3.631	3.659	3.588	3.651	
	ALL	1.76	1.771	3.954	1.88	1.834	1.736	1.728	1.833	2.313

Scenario 1		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.989	0.496	1	0.989	0.36	0.995	0.96	0.225	0.94
	TNR	0.989	0.979	0.993	0.989	0.993	1	0.989	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									
labeltab:s1d1										

Table 5: Scenario 1, $\delta = 0.9$

H.2 Scenario 2

Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.958	0.779	1	0.957	0.686	0.984	0.801	0.569	0.843
	TNR	0.991	0.925	0.949	0.992	0.964	0.992	0.997	0.985	1
	SFE	0	0.01	0	0	0.003	0	0	0	0
	SUB	3.738	3.729	3.629	3.745	3.76	3.913	3.778	3.744	3.243
	ALL	2.708	2.742	3.079	2.693	2.82	2.529	2.72	2.724	2.737
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.96	0.793	0.978	0.959	0.699	0.921	0.854	0.578	0.738
	TNR	0.986	0.928	1	0.987	0.969	1	0.987	0.992	1
	SFE	0	0.004	0	0	0.001	0	0	0	0
	SUB	3.693	3.672	3.457	3.756	3.718	4.226	3.742	3.757	4.082
	ALL	2.749	2.76	2.899	2.805	2.768	3.183	2.699	2.785	3.302
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.956	0.782	0.941	0.956	0.687	0.896	0.9	0.568	0.618
	TNR	0.995	0.941	0.979	0.995	0.975	0.991	0.995	0.991	0.998
	SFE	0	0.006	0	0	0.002	0	0	0	0
	SUB	3.767	3.742	3.335	3.763	3.696	4.337	3.787	3.765	3.909
	ALL	2.73	2.733	2.657	2.8	2.842	3.125	2.747	2.762	3.047
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.955	0.785	0.934	0.955	0.691	0.933	0.954	0.576	0.933
	TNR	0.998	0.96	1	0.998	0.982	1	0.998	0.993	1
	SFE	0	0.002	0	0	0	0	0	0	0
	SUB	3.76	3.696	3.659	3.732	3.73	3.918	3.752	3.774	3.719
	ALL	2.719	2.697	2.671	2.718	2.75	2.216	2.734	2.822	2.866

Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.955	0.792	0.933	0.955	0.696	0.933	0.955	0.58	0.899
	TNR	0.995	0.973	1	0.995	0.992	1	0.995	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.781	3.744	3.62	3.727	3.754	3.638	3.756	3.811	4.313
	ALL	2.728	2.725	1.902	2.829	2.766	2.538	2.755	2.784	2.837
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.952	0.798	0.933	0.952	0.701	0.933	0.952	0.584	0.918
	TNR	1	0.976	1	1	0.992	1	1	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.84	3.686	3.124	3.757	3.745	3.945	3.695	3.727	4.462
	ALL	2.744	2.77	1.968	2.764	2.773	3.536	2.774	2.818	2.542
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.957	0.798	0.933	0.957	0.7	0.933	0.938	0.581	0.933
	TNR	1	0.976	1	1	0.993	1	1	0.998	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.762	3.607	3.583	3.693	3.663	3.557	3.771	3.787	3.997
	ALL	2.776	2.605	2.475	2.795	2.831	1.583	2.791	2.736	3.102
Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.956	0.81	0.934	0.956	0.71	0.933	0.946	0.589	0.907
	TNR	0.998	0.975	1	0.998	0.994	1	0.998	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.783	3.793	5.313	3.736	3.708	3.45	3.659	3.715	2.868
	ALL	2.78	2.57	2.35	2.838	2.792	3.763	2.817	2.661	1.782

Scenario 2		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.954	0.8	0.933	0.954	0.701	0.933	0.954	0.582	0.933
	TNR	1	0.985	1	1	0.998	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 6: Scenario 2, $\delta = 0.5$

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.932	0.674	0.996	0.92	0.57	0.949	0.762	0.447	0.743
	TNR	0.997	0.972	0.988	0.998	0.987	1	0.998	0.995	1
	SFE	0	0.003	0	0	0	0	0	0	0
	SUB	3.767	3.782	3.559	3.758	3.761	3.613	3.798	3.737	4.028
	ALL	2.668	2.733	2.978	2.783	2.782	2.401	2.781	2.791	2.958
Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.928	0.696	0.931	0.927	0.59	0.827	0.824	0.46	0.52
	TNR	0.997	0.976	1	0.997	0.993	1	0.997	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.765	3.758	4	3.763	3.762	3.828	3.738	3.718	3.63
	ALL	2.751	2.805	2.863	2.783	2.745	2.442	2.763	2.743	3.164
Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.94	0.694	0.928	0.94	0.591	0.81	0.872	0.467	0.465
	TNR	0.997	0.977	0.994	0.997	0.991	1	0.997	0.997	1
	SFE	0	0.002	0	0	0	0	0	0	0
	SUB	3.723	3.732	3.702	3.733	3.708	4.038	3.749	3.733	3.866
	ALL	2.716	2.775	2.635	2.817	2.853	2.635	2.782	2.678	2.531
Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.935	0.703	0.933	0.935	0.603	0.933	0.917	0.484	0.923
	TNR	0.998	0.983	1	0.998	0.993	1	0.998	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.732	3.772	3.546	3.74	3.73	4.178	3.768	3.771	3.713
	ALL	2.772	2.663	3.011	2.721	2.737	2.055	2.757	2.745	2.934

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.934	0.714	0.933	0.934	0.613	0.93	0.934	0.492	0.829
	TNR	0.998	0.992	1	0.998	0.998	1	0.998	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.737	3.765	3.746	3.709	3.714	3.039	3.71	3.796	3.678
	ALL	2.709	2.632	3.461	2.853	2.709	2.83	2.777	2.716	4.246

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.935	0.722	0.933	0.935	0.62	0.933	0.925	0.5	0.845
	TNR	1	0.992	1	1	0.998	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.749	3.742	3.862	3.688	3.737	3.714	3.715	3.783	3.82
	ALL	2.706	2.697	2.601	2.711	2.762	2.443	2.793	2.662	2.519

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.937	0.724	0.933	0.936	0.621	0.933	0.917	0.5	0.933
	TNR	1	0.992	1	1	0.998	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.735	3.763	3.413	3.818	3.715	4.082	3.739	3.68	4.011
	ALL	2.665	2.735	2.211	2.685	2.761	3.09	2.761	2.653	2.913

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.94	0.74	0.933	0.94	0.635	0.926	0.93	0.511	0.876
	TNR	1	0.993	1	1	0.998	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.758	3.772	3.708	3.655	3.815	3.597	3.689	3.708	5.138
	ALL	2.9	2.761	2.544	2.66	2.668	2.208	2.793	2.927	1.894

Scenario 2		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.94	0.732	0.933	0.94	0.629	0.933	0.94	0.507	0.933
	TNR	1	0.997	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 7: Scenario 2, $\delta = 0.7$

Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.882	0.497	0.966	0.85	0.387	0.834	0.654	0.268	0.578
	TNR	1	0.995	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.745	3.728	3.336	3.755	3.759	3.605	3.766	3.754	3.413
	ALL	2.754	2.762	2.212	2.682	2.814	2.734	2.713	2.838	2.783
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.882	0.53	0.814	0.865	0.413	0.585	0.748	0.284	0.195
	TNR	1	0.998	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.771	3.747	3.768	3.741	3.742	3.746	3.785	3.77	3.601
	ALL	2.722	2.793	2.806	2.73	2.691	2.013	2.745	2.781	3.432
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.907	0.548	0.857	0.907	0.437	0.612	0.809	0.311	0.278
	TNR	0.998	0.995	1	0.998	0.998	1	0.998	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.768	3.802	3.572	3.781	3.748	3.705	3.747	3.72	3.357
	ALL	2.823	2.822	2.581	2.682	2.753	1.972	2.751	2.763	2.731
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.897	0.572	0.933	0.897	0.465	0.928	0.87	0.342	0.858
	TNR	1	0.996	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.792	3.718	3.191	3.756	3.707	3.754	3.729	3.76	3.702
	ALL	2.762	2.749	2.469	2.73	2.78	2.714	2.784	2.785	2.994

Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.902	0.589	0.931	0.902	0.481	0.89	0.893	0.355	0.666
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.723	3.76	4.286	3.777	3.734	3.495	3.83	3.721	3.932
	ALL	2.719	2.694	2.857	2.746	2.709	2.883	2.681	2.745	2.753
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.911	0.603	0.933	0.911	0.495	0.921	0.893	0.367	0.575
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.795	3.806	4.137	3.706	3.704	3.731	3.662	3.768	3.986
	ALL	2.746	2.776	2.11	2.823	2.741	1.671	2.727	2.742	1.255
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.913	0.608	0.933	0.913	0.5	0.933	0.894	0.374	0.932
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.71	3.666	3.635	3.767	3.802	3.378	3.764	3.727	3.821
	ALL	2.783	2.716	2.951	2.721	2.758	2.562	2.674	2.67	3.094
Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.915	0.63	0.932	0.915	0.52	0.906	0.906	0.389	0.778
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.799	3.732	4.021	3.757	3.772	4.385	3.828	3.741	3.443
	ALL	2.914	2.647	3.573	2.852	2.723	1.043	2.71	2.595	1.892

Scenario 2		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.917	0.626	0.933	0.917	0.519	0.933	0.917	0.392	0.926
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 8: Scenario 2, $\delta = 0.9$

H.3 Scenario 3

Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.848	0.774	0.846	0.784	0.677	0.725	0.522	0.549	0.514
	TNR	0.672	0.827	0.977	0.707	0.91	1	0.857	0.965	1
	SFE	0	0.012	0	0	0.004	0	0	0.001	0
	SUB	3.737	3.628	3.964	3.728	3.692	3.755	3.728	3.757	4.011
	ALL	3.01	2.94	3.306	2.898	2.939	2.971	2.931	2.956	3.1
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.865	0.791	0.854	0.785	0.692	0.674	0.591	0.556	0.41
	TNR	0.694	0.817	1	0.728	0.902	1	0.834	0.959	1
	SFE	0	0.007	0	0	0.001	0	0	0	0
	SUB	3.73	3.66	3.661	3.714	3.733	3.848	3.788	3.729	3.713
	ALL	2.92	2.979	2.912	2.902	2.977	2.965	2.906	2.901	3.683
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.873	0.79	0.957	0.84	0.688	0.875	0.647	0.553	0.611
	TNR	0.814	0.847	0.994	0.821	0.923	1	0.894	0.97	1
	SFE	0	0.008	0	0	0.002	0	0	0.001	0
	SUB	3.721	3.641	3.593	3.731	3.676	3.63	3.745	3.749	3.934
	ALL	3.004	2.863	2.746	2.912	2.996	2.897	2.96	2.985	2.343
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.921	0.805	0.98	0.883	0.698	0.947	0.748	0.555	0.814
	TNR	0.873	0.874	0.998	0.877	0.946	1	0.922	0.984	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.748	3.596	3.555	3.686	3.688	3.543	3.707	3.75	3.915
	ALL	2.965	2.972	3.654	2.932	3.022	2.616	2.995	2.979	3.097

Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.912	0.802	0.978	0.882	0.698	0.964	0.783	0.561	0.907
	TNR	0.939	0.894	1	0.94	0.958	1	0.95	0.988	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.765	3.635	3.625	3.665	3.717	3.605	3.651	3.805	3.784
	ALL	2.905	2.992	3.005	2.965	2.974	3.461	2.918	2.983	3.448
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.945	0.824	0.96	0.927	0.718	0.944	0.831	0.573	0.885
	TNR	0.937	0.867	1	0.94	0.944	1	0.953	0.983	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.719	3.621	3.318	3.647	3.612	3.264	3.626	3.687	3.539
	ALL	3.062	3.122	3.532	2.936	2.979	2.767	2.863	2.914	2.581
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.942	0.807	0.988	0.927	0.701	0.96	0.835	0.559	0.922
	TNR	0.972	0.897	0.975	0.973	0.96	0.998	0.979	0.989	1
	SFE	0	0.002	0	0	0	0	0	0	0
	SUB	3.594	3.615	3.895	3.596	3.696	4.859	3.604	3.713	3.733
	ALL	3.004	3.061	2.356	2.883	2.976	2.882	2.988	2.942	2.785
Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.948	0.818	0.971	0.932	0.71	0.966	0.863	0.566	0.908
	TNR	0.969	0.893	1	0.969	0.963	1	0.983	0.993	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.394	3.638	4.028	3.365	3.623	4.461	3.487	3.75	2.778
	ALL	3.148	2.859	3.327	3.095	3.107	3.299	2.992	2.937	2.465

Scenario 3		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.959	0.821	0.939	0.945	0.711	0.938	0.875	0.566	0.938
	TNR	0.983	0.898	1	0.984	0.965	1	0.987	0.993	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 9: Scenario 3, $\delta = 0.5$

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.804	0.658	0.759	0.728	0.546	0.611	0.449	0.411	0.404
	TNR	0.719	0.919	1	0.755	0.965	1	0.902	0.989	1
	SFE	0	0.003	0	0	0.001	0	0	0	0
	SUB	3.735	3.702	3.586	3.703	3.719	3.697	3.738	3.782	3.876
	ALL	2.988	2.984	3.398	2.937	2.948	2.909	2.964	2.94	3.393
Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.828	0.677	0.683	0.739	0.56	0.505	0.541	0.419	0.222
	TNR	0.736	0.907	1	0.764	0.956	1	0.861	0.985	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.666	3.628	3.849	3.74	3.754	4.139	3.691	3.772	3.544
	ALL	2.987	2.984	2.661	3.046	2.961	3.856	2.937	3.008	2.987
Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.839	0.686	0.902	0.791	0.57	0.766	0.581	0.431	0.482
	TNR	0.838	0.921	1	0.844	0.966	1	0.905	0.99	1
	SFE	0	0.002	0	0	0.001	0	0	0	0
	SUB	3.738	3.71	3.802	3.765	3.727	3.681	3.73	3.697	3.625
	ALL	2.937	2.939	2.221	2.932	2.977	2.807	2.925	2.939	2.2
Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.891	0.702	0.961	0.846	0.58	0.902	0.692	0.436	0.683
	TNR	0.896	0.94	1	0.896	0.979	1	0.937	0.995	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.715	3.655	3.524	3.724	3.729	3.846	3.724	3.746	3.685
	ALL	2.99	3.008	3.01	3.011	2.89	2.237	2.974	2.914	3.058

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.884	0.707	0.967	0.843	0.591	0.938	0.719	0.451	0.791
	TNR	0.958	0.951	1	0.958	0.983	1	0.964	0.996	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.658	3.701	3.679	3.718	3.72	3.759	3.697	3.702	3.856
	ALL	2.942	2.993	3.032	2.948	2.994	2.506	2.859	3.009	2.49

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.919	0.731	0.948	0.893	0.61	0.922	0.753	0.462	0.686
	TNR	0.966	0.932	1	0.973	0.976	1	0.978	0.995	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.702	3.606	3.262	3.645	3.754	3.067	3.671	3.729	4.37
	ALL	2.991	2.908	2.801	2.91	2.941	2.471	2.928	2.94	3.064

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.921	0.72	0.964	0.895	0.601	0.939	0.784	0.457	0.861
	TNR	0.981	0.948	0.996	0.981	0.983	1	0.984	0.996	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.557	3.725	3.989	3.607	3.702	4.419	3.513	3.738	3.031
	ALL	2.922	3.025	3.342	3.046	2.95	4.192	2.9	2.868	1.854

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.928	0.734	0.967	0.908	0.614	0.933	0.827	0.466	0.803
	TNR	0.977	0.948	1	0.977	0.987	1	0.987	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.469	3.645	3.52	3.618	3.705	3.681	3.498	3.7	2.095
	ALL	3.006	2.883	4.234	2.944	2.842	4.098	3.016	3.04	2.485

Scenario 3		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.941	0.738	0.938	0.928	0.616	0.938	0.842	0.47	0.934
	TNR	0.99	0.949	1	0.99	0.986	1	0.994	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 10: Scenario 3, $\delta = 0.7$

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.734	0.462	0.601	0.589	0.347	0.422	0.335	0.228	0.242
	TNR	0.781	0.98	1	0.836	0.993	1	0.936	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.728	3.708	3.811	3.729	3.778	3.711	3.765	3.756	3.681
	ALL	2.909	2.978	3.007	3.005	2.985	2.763	2.98	2.907	3.24

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.744	0.484	0.482	0.654	0.363	0.275	0.435	0.239	0.05
	TNR	0.791	0.972	1	0.808	0.99	1	0.894	0.998	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.746	3.754	4.101	3.7	3.669	3.635	3.705	3.782	3.514
	ALL	2.975	3.005	3.285	2.972	3.012	2.889	2.945	2.968	3.128

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.769	0.513	0.787	0.724	0.393	0.552	0.479	0.265	0.321
	TNR	0.874	0.977	1	0.875	0.993	1	0.934	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.78	3.716	3.508	3.726	3.751	3.76	3.715	3.814	4.111
	ALL	2.919	2.994	3.04	2.982	2.989	2.222	2.944	2.941	2.748

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.832	0.532	0.904	0.79	0.408	0.761	0.62	0.278	0.465
	TNR	0.906	0.985	1	0.906	0.996	1	0.954	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.709	3.707	3.8	3.718	3.765	3.805	3.716	3.787	3.207
	ALL	3.003	2.862	3.417	2.927	3.023	3.13	2.941	2.978	3.356

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.838	0.551	0.928	0.787	0.432	0.84	0.635	0.302	0.519
	TNR	0.971	0.987	1	0.971	0.996	1	0.973	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.747	3.733	3.553	3.692	3.738	4.195	3.683	3.823	4.086
	ALL	3.025	2.927	2.776	2.924	2.946	2.426	2.957	2.949	3.277
Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.886	0.576	0.921	0.85	0.449	0.859	0.7	0.308	0.192
	TNR	0.973	0.979	1	0.979	0.995	1	0.983	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.679	3.774	3.978	3.669	3.759	3.147	3.745	3.784	3.583
	ALL	3.014	2.973	2.312	2.983	2.879	2.482	3.009	2.933	2.587
Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.883	0.576	0.936	0.861	0.453	0.88	0.697	0.319	0.739
	TNR	0.987	0.984	1	0.987	0.996	1	0.987	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.643	3.72	4.149	3.691	3.768	3.456	3.715	3.705	3.178
	ALL	2.99	2.922	2.248	2.985	3.127	2.074	2.819	2.911	2.537
Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.899	0.595	0.92	0.872	0.468	0.824	0.777	0.328	0.605
	TNR	0.98	0.986	1	0.98	0.998	1	0.989	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.703	3.783	3.798	3.588	3.761	3.405	3.495	3.675	4.274
	ALL	2.936	2.958	1.412	2.932	3.041	2.638	2.83	2.989	2.022

Scenario 3		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.913	0.602	0.938	0.886	0.476	0.937	0.77	0.338	0.872
	TNR	0.997	0.985	1	0.997	0.997	1	0.997	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 11: Scenario 3, $\delta = 0.9$

H.4 Scenario 4

Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.91	0.759	0.554	0.774	0.619	0.225	0.603	0.447	0
	TNR	0.998	0.995	1	0.998	0.997	1	0.999	0.999	1
	SFE	0	0.001	0	0	0	0	0	0	0
	SUB	3.574	3.394	3.701	3.604	3.573	3.844	3.627	3.696	3.745
	ALL	1.428	1.508	1.682	1.436	1.461	1.18	1.443	1.412	1.836
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.956	0.796	0.44	0.867	0.656	0.005	0.629	0.469	0
	TNR	0.998	0.995	1	0.998	0.997	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.617	3.35	3.777	3.582	3.573	3.352	3.633	3.668	3.408
	ALL	1.373	1.487	2.131	1.365	1.503	1.551	1.468	1.443	1.308
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.986	0.799	0.885	0.935	0.657	0.413	0.683	0.464	0.073
	TNR	0.998	0.995	1	0.998	0.997	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.612	3.361	3.995	3.601	3.525	3.825	3.671	3.628	3.758
	ALL	1.405	1.451	2.255	1.462	1.35	1.95	1.463	1.358	0.916
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.993	0.789	1	0.961	0.632	1	0.685	0.425	1
	TNR	0.999	0.996	0.964	0.999	0.998	0.964	0.999	0.999	0.964
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.514	3.363	3.765	3.607	3.579	3.997	3.617	3.681	3.496
	ALL	1.415	1.457	1.349	1.409	1.472	1.561	1.462	1.484	1.846

Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.994	0.797	1	0.945	0.644	0.999	0.746	0.434	0.261
	TNR	0.999	0.996	1	0.999	0.998	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.609	3.398	3.669	3.548	3.57	4.33	3.706	3.644	4
	ALL	1.54	1.442	1.042	1.421	1.339	1.077	1.375	1.477	1.171
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.995	0.826	1	0.976	0.668	1	0.855	0.447	0.989
	TNR	0.998	0.996	1	0.998	0.998	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.598	3.391	3.338	3.613	3.549	3.321	3.613	3.568	3.796
	ALL	1.457	1.516	1.848	1.487	1.322	0.955	1.486	1.275	1.636
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.996	0.828	1	0.986	0.676	1	0.876	0.47	1
	TNR	0.999	0.996	1	0.999	0.998	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.589	3.317	2.716	3.639	3.547	3.927	3.559	3.628	3.88
	ALL	1.45	1.299	0.442	1.387	1.411	1.724	1.412	1.39	1.624
Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.998	0.833	1	0.987	0.689	1	0.877	0.478	0.993
	TNR	0.999	0.996	0.964	0.999	0.998	0.964	0.999	1	0.969
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.497	3.175	3.202	3.459	3.581	2.617	3.579	3.55	
	ALL	1.634	1.513	2.677	1.305	1.502	1.313	1.335	1.471	2.66

Scenario 4		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	1	0.841	1	1	0.675	1	0.92	0.45	1
	TNR	0.998	0.996	0.964	0.998	0.999	0.974	0.999	1	0.992
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 12: Scenario 4, $\delta = 0.5$

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.855	0.601	0.336	0.753	0.452	0	0.541	0.287	0
	TNR	0.999	0.997	1	0.999	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.706	3.54	3.79	3.641	3.701	4.034	3.646	3.697	3.857
	ALL	1.408	1.394	0.785	1.437	1.41	1.98	1.418	1.509	0.865
Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.928	0.65	0.193	0.851	0.486	0	0.568	0.301	0
	TNR	0.998	0.998	1	0.998	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.646	3.57	3.302	3.687	3.682	3.615	3.679	3.755	3.501
	ALL	1.382	1.343	1.039	1.449	1.341	1.21	1.462	1.378	1.342
Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.977	0.662	0.652	0.89	0.495	0.186	0.586	0.303	0.006
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.674	3.525	3.763	3.65	3.537	3.334	3.69	3.724	3.632
	ALL	1.452	1.433	1.951	1.417	1.345	1.863	1.432	1.436	1.592
Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.982	0.653	1	0.938	0.47	1	0.629	0.272	1
	TNR	0.999	0.998	0.964	0.999	0.999	0.964	1	1	0.964
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.683	3.575	4.183	3.67	3.687	4.021	3.637	3.692	4.462
	ALL	1.423	1.383	1.702	1.33	1.434	1.453	1.468	1.41	1.355

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.989	0.67	1	0.932	0.489	0.805	0.692	0.281	0.004
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.644	3.553	4.073	3.678	3.679	3.87	3.638	3.683	4.08
	ALL	1.411	1.407	1.555	1.426	1.428	1.675	1.37	1.426	1.195

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.99	0.701	1	0.961	0.511	1	0.811	0.285	0.888
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.681	3.592	3.561	3.648	3.611	2.799	3.682	3.698	3.301
	ALL	1.369	1.424	0.957	1.407	1.46	2.053	1.469	1.455	1.595

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.989	0.714	1	0.979	0.538	1	0.839	0.326	0.994
	TNR	0.999	0.997	1	0.999	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.63	3.594	4.071	3.651	3.635	3.851	3.744	3.756	3.432
	ALL	1.337	1.355	2.481	1.511	1.361	1.225	1.46	1.389	3.454

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.996	0.734	1	0.976	0.559	1	0.856	0.339	0.974
	TNR	0.999	0.998	0.964	0.999	0.999	0.967	0.999	1	0.99
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.546	3.505	4.782	3.528	3.589		3.618	3.615	
	ALL	1.311	1.317	-0.397	1.456	1.464	1.639	1.314	1.372	3.094

Scenario 4		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.999	0.731	1	0.998	0.532	1	0.889	0.306	1
	TNR	0.999	0.998	0.973	0.999	0.999	0.983	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 13: Scenario 4, $\delta = 0.7$

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.818	0.356	0	0.683	0.219	0	0.416	0.108	0
	TNR	0.999	0.999	1	0.999	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.72	3.679	3.792	3.71	3.756	3.937	3.667	3.768	3.903
	ALL	1.395	1.362	1.803	1.414	1.407	1.665	1.4	1.461	1.642
Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.899	0.394	0	0.784	0.244	0	0.483	0.113	0
	TNR	0.999	0.999	1	0.999	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.694	3.721	3.174	3.723	3.663	3.615	3.725	3.679	4.039
	ALL	1.39	1.432	1.691	1.369	1.466	1.642	1.441	1.435	1.189
Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.944	0.426	0.261	0.829	0.258	0.021	0.519	0.114	0
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.74	3.615	3.528	3.72	3.696	4.053	3.677	3.703	3.83
	ALL	1.422	1.424	1.492	1.425	1.428	1.232	1.39	1.374	1.765
Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.945	0.406	1	0.894	0.244	1	0.487	0.108	0.973
	TNR	1	0.999	0.964	1	1	0.965	1	1	0.979
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.705	3.677	3.845	3.682	3.673	3.851	3.751	3.685	3.285
	ALL	1.429	1.377	1.556	1.45	1.458	1.81	1.387	1.372	1.69

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.958	0.441	0.83	0.893	0.26	0.039	0.646	0.108	0
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.732	3.723	3.657	3.767	3.766	3.812	3.739	3.72	
	ALL	1.436	1.501	1.589	1.426	1.507	1.317	1.435	1.463	1.437

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.98	0.472	1	0.932	0.274	0.927	0.717	0.115	0.491
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.698	3.694	3.196	3.686	3.703	3.359	3.762	3.728	3.321
	ALL	1.389	1.42	0.609	1.359	1.362	0.342	1.339	1.203	0.931

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.979	0.511	1	0.959	0.324	0.998	0.783	0.153	0.956
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.787	3.647	3.957	3.726	3.687	3.589	3.828	3.72	
	ALL	1.358	1.402	2.16	1.45	1.436	0.95	1.544	1.392	1.439

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.984	0.54	1	0.955	0.346	0.986	0.776	0.162	0.903
	TNR	1	0.999	0.967	1	1	0.983	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.752	3.652		3.651	3.795		3.582	3.598	
	ALL	1.323	1.325	3.546	1.513	1.452	0.023	1.47	1.27	1.701

Scenario 4		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.995	0.521	1	0.995	0.32	1	0.786	0.145	0.947
	TNR	1	1	0.996	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 14: Scenario 4, $\delta = 0.9$

H.5 Scenario 5

Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.848	0.456	0.368	0.657	0.326	0.147	0.399	0.198	0
	TNR	1	0.998	1	1	0.999	1	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.762	2.602	3.505	3.749	2.653	3.402	3.77	2.549	3.766
	ALL	1.984	1.96	1.961	2.015	1.912	2.188	1.932	2.049	1.735
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.843	0.466	0.413	0.703	0.335	0.245	0.507	0.2	0.143
	TNR	1	0.998	0.797	1	0.999	0.819	1	0.999	0.979
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.772	2.575	3.47	3.785	2.445	3.444	3.74	2.577	3.79
	ALL	2.001	2.006	2.065	1.913	1.981	2.096	2.062	2.008	2.503
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.888	0.428	0.656	0.823	0.295	0.363	0.53	0.164	0.191
	TNR	1	0.998	1	1	0.999	1	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.773	2.494	4.001	3.751	2.374	3.82	3.739	2.445	3.879
	ALL	1.949	2.024	3.017	2.034	2.008	2.992	2.044	2.069	1.971
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.946	0.429	0.981	0.87	0.275	0.947	0.586	0.147	0.668
	TNR	1	0.998	0.763	1	0.999	0.785	1	0.999	0.967
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.769	2.579	3.689	3.709	2.68	3.647	3.735	2.536	3.217
	ALL	2.029	1.943	1.692	1.921	1.984	1.983	1.966	2.004	2.047

Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.969	0.486	0.667	0.92	0.316	0.667	0.7	0.156	0.565
	TNR	1	0.998	1	1	0.999	1	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.791	2.545	3.822	3.779	2.312	3.504	3.795	2.262	3.731
	ALL	1.98	2.004	2.345	2.022	2.039	2.479	2.044	2.047	1.747
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.957	0.463	1	0.903	0.304	0.82	0.69	0.139	0.094
	TNR	1	0.998	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.626	2.497	3.472	3.724	2.546	4.012	3.705	2.374	3.39
	ALL	1.93	1.963	1.292	1.976	1.998	2.331	1.984	1.99	1.132
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.983	0.468	1	0.933	0.308	1	0.803	0.152	0.741
	TNR	1	0.998	1	1	0.999	1	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.723	2.527	4.277	3.787	2.499	3.544	3.79	2.569	3.836
	ALL	1.986	1.974	2.802	2.066	1.936	0.673	1.942	2.04	2.673
Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.987	0.498	1	0.957	0.325	0.972	0.823	0.15	0.749
	TNR	1	0.998	0.819	1	0.999	0.891	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.679	2.41	2.799	3.649	2.433	1.645	3.668	2.487	2.292
	ALL	2.14	2.082	2.721	2.034	1.826	2.295	1.911	1.88	2.933

Scenario 5		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.99	0.481	0.865	0.937	0.315	0.72	0.813	0.143	0.402
	TNR	1	0.998	1	1	0.999	1	1	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 15: Scenario 5, $\delta = 0.5$

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.818	0.276	0.201	0.627	0.173	0.036	0.319	0.086	0
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.761	2.709	3.757	3.778	2.62	3.456	3.762	2.523	4.192
	ALL	1.968	2.003	2.133	2	2.003	2.012	1.909	1.945	2.094

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.807	0.303	0.247	0.676	0.187	0.183	0.437	0.086	0.037
	TNR	1	0.999	0.816	1	0.999	0.964	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.736	2.535	3.815	3.771	2.522	3.62	3.756	2.327	3.436
	ALL	2.027	2.004	2.375	1.894	2.01	1.741	2.004	2.037	2.127

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.858	0.27	0.466	0.767	0.16	0.2	0.457	0.067	0.156
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.752	2.461	3.764	3.731	2.454	3.874	3.751	2.275	3.376
	ALL	1.986	2.053	1.621	2.018	1.961	2.517	1.97	1.958	1.66

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.926	0.253	0.951	0.84	0.146	0.749	0.56	0.07	0.504
	TNR	1	0.999	0.785	1	0.999	0.935	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.729	2.682	3.875	3.772	2.681	3.813	3.684	2.553	3.8
	ALL	2.027	1.868	1.593	1.949	2.03	2.443	2.003	2.049	2.069

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.962	0.304	0.667	0.897	0.166	0.667	0.647	0.061	0.273
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.783	2.518	3.136	3.691	2.3	3.351	3.75	2.299	3.9
	ALL	2.014	2.099	1.983	2.004	2.024	2.044	1.977	1.989	2.618

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.953	0.3	0.999	0.877	0.157	0.24	0.63	0.056	0.005
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.707	2.629	3.007	3.722	2.548	4.15	3.749	2.567	3.624
	ALL	2.03	1.927	1.011	1.97	2.014	3.328	1.916	1.957	0.729

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.983	0.309	1	0.917	0.171	0.963	0.767	0.069	0.615
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.775	2.695	4.278	3.787	2.587	3.78	3.85	2.439	4.438
	ALL	2.06	1.935	0.611	1.917	2.062	2.559	1.928	1.868	2.356

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.983	0.337	0.988	0.94	0.178	0.908	0.767	0.07	0.669
	TNR	1	0.999	0.871	1	0.999	0.99	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.722	2.669	2.226	3.803	2.753	2.77	3.803	2.591	3.369
	ALL	1.889	2.062	3.994	1.848	1.791	2.181	2.054	1.921	2.542

Scenario 5		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.98	0.33	0.76	0.927	0.177	0.543	0.78	0.059	0.259
	TNR	1	0.999	1	1	0.999	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 16: Scenario 5, $\delta = 0.7$

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.708	0.094	0.069	0.558	0.047	0	0.245	0.017	0
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.74	2.793	3.427	3.729	2.621	3.865	3.778	2.152	3.473
	ALL	1.959	2.046	1.892	1.922	1.951	2.108	1.938	2.022	2.025
Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.762	0.109	0.168	0.616	0.051	0.03	0.383	0.016	0
	TNR	1	1	0.998	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.728	2.494	3.079	3.743	2.516	3.946	3.798	2.379	3.649
	ALL	1.998	2.023	1.824	2.019	1.979	1.892	1.963	2.026	2.543
Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.843	0.097	0.193	0.71	0.039	0.156	0.36	0.009	0.009
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.747	2.497	3.839	3.774	2.51	3.186	3.837	1.909	3.557
	ALL	2.043	1.962	1.891	1.946	2.05	1.927	2.004	1.939	1.451
Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.902	0.099	0.689	0.75	0.054	0.489	0.47	0.022	0.187
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.756	2.862	4.029	3.783	2.777	3.378	3.724	2.491	
	ALL	2.033	2.041	1.899	2.018	1.972	1.427	1.935	1.963	2.62

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.945	0.111	0.665	0.867	0.042	0.375	0.573	0.01	0.002
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.71	2.564	3.774	3.734	2.455	3.574	3.721	2.245	3.346
	ALL	1.994	2.057	2.714	1.978	1.988	2.394	2.07	1.986	2.178

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.95	0.109	0.293	0.837	0.041	0.002	0.587	0.01	0
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.753	2.657	2.796	3.761	2.689	3.804	3.689	2.805	4.549
	ALL	1.974	1.999	2.738	1.928	2.044	2.658	1.988	1.943	2.839

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.973	0.128	0.967	0.9	0.056	0.637	0.71	0.013	0.309
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.717	2.606	3.352	3.756	2.396	4.44	3.799	2.093	3.279
	ALL	2.138	2.124	1.805	1.902	2.023	2.573	1.921	1.884	1.92

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.977	0.138	0.928	0.923	0.061	0.735	0.663	0.016	0.548
	TNR	1	0.999	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.783	2.539	2.611	3.689	2.614	2.076	3.787	1.983	
	ALL	1.766	1.88	0.602	2.065	1.979	2.116	1.968	1.899	1.422

Scenario 5		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.97	0.14	0.529	0.897	0.051	0.31	0.73	0.01	0.057
	TNR	1	1	1	1	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 17: Scenario 5, $\delta = 0.9$

H.6 Scenario 6

Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.822	0.84	0.942	0.787	0.742	0.843	0.611	0.589	0.61
	TNR	0.998	0.998	0.454	0.998	0.998	0.54	0.999	0.999	0.718
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.546	3.428	3.142	3.534	3.6	3.145	3.573	3.678	3.45
	ALL	3.166	3.168	3.269	3.184	3.198	3.269	3.106	3.197	3.272
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.863	0.855	0.969	0.847	0.759	0.844	0.742	0.599	0.619
	TNR	0.998	0.998	0.698	0.998	0.999	0.934	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.593	3.41	3.707	3.564	3.562	3.631	3.615	3.677	4.104
	ALL	3.202	3.155	3.179	3.168	3.184	3.139	3.177	3.219	3.065
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.88	0.849	0.803	0.841	0.748	0.797	0.707	0.595	0.32
	TNR	0.998	0.998	1	0.998	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.564	3.444	3.816	3.627	3.621	3.422	3.663	3.647	4.159
	ALL	3.158	3.127	3.52	3.173	3.119	3.327	3.162	3.158	2.76
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.884	0.877	0.83	0.851	0.785	0.814	0.741	0.624	0.803
	TNR	0.998	0.998	0.916	0.999	0.998	0.967	0.999	0.999	0.993
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.606	3.44	3.562	3.563	3.525	3.405	3.614	3.647	3.899
	ALL	3.162	3.179	2.856	3.212	3.219	3.35	3.178	3.133	3.517

Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.892	0.876	0.885	0.875	0.777	0.829	0.781	0.615	0.773
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.553	3.397	3.563	3.586	3.565	3.513	3.6	3.618	4.284
	ALL	3.319	3.139	2.734	3.206	3.099	4.108	3.154	3.126	3.745
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.884	0.886	0.8	0.876	0.795	0.8	0.782	0.629	0.8
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.562	3.441	3.839	3.592	3.477	3.374	3.528	3.721	3.233
	ALL	3.192	3.167	2.583	3.222	3.14	3.035	3.082	3.102	4.258
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.886	0.882	0.89	0.86	0.791	0.821	0.803	0.625	0.8
	TNR	0.999	0.998	1	0.999	0.999	1	0.999	0.999	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.461	3.426	3.487	3.582	3.678	3.756	3.534	3.697	4.196
	ALL	3.245	3.111	2.273	3.221	3.178	3.667	3.119	3.183	2.363
Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.891	0.886	0.875	0.87	0.797	0.858	0.827	0.646	0.826
	TNR	0.999	0.998	0.751	0.999	0.999	0.893	0.999	1	0.981
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.603	3.51	2.261	3.449	3.447	3.404	3.632	3.3	3.183
	ALL	3.294	3.288	4.059	3.262	3.153	4.711	3.227	3.237	3.597

Scenario 6		LRV								
	$\delta = 0.5$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.898	0.892	0.975	0.89	0.8	0.905	0.805	0.635	0.86
	TNR	0.999	0.998	0.497	0.999	0.999	0.677	0.999	0.999	0.805
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 18: Scenario 6, $\delta = 0.5$

Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.782	0.721	0.901	0.755	0.589	0.735	0.534	0.414	0.495
	TNR	0.999	0.999	0.533	0.999	0.999	0.703	0.999	1	0.958
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.629	3.51	3.595	3.647	3.627	3.452	3.672	3.692	3.737
	ALL	3.179	3.123	3.538	3.211	3.176	2.844	3.192	3.148	3.334
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.837	0.745	0.876	0.818	0.611	0.688	0.677	0.436	0.491
	TNR	0.998	0.999	0.922	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.556	3.515	3.258	3.595	3.675	3.718	3.651	3.707	3.863
	ALL	3.15	3.18	2.999	3.166	3.194	2.64	3.211	3.186	2.573
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.847	0.751	0.802	0.791	0.622	0.737	0.675	0.452	0.241
	TNR	0.999	0.999	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.578	3.525	3.747	3.632	3.651	3.689	3.622	3.731	3.785
	ALL	3.142	3.154	3.838	3.146	3.159	3.387	3.192	3.2	3.729
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.853	0.789	0.816	0.828	0.662	0.803	0.708	0.467	0.8
	TNR	0.999	0.998	0.963	0.999	0.999	0.993	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.574	3.511	3.66	3.588	3.634	3.348	3.598	3.754	4.17
	ALL	3.173	3.208	3.06	3.189	3.209	3.164	3.213	3.163	3.069

Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.857	0.787	0.857	0.828	0.657	0.804	0.732	0.464	0.707
	TNR	0.999	0.999	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.627	3.553	3.704	3.595	3.666	3.503	3.679	3.684	3.613
	ALL	3.11	3.136	3.589	3.118	3.165	3.427	3.169	3.228	2.946
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.866	0.808	0.8	0.853	0.676	0.8	0.752	0.493	0.8
	TNR	0.999	0.999	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.513	3.509	3.748	3.576	3.566	4.144	3.597	3.666	4.151
	ALL	3.154	3.241	4.027	3.14	3.231	2.995	3.2	3.214	3.238
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.863	0.808	0.846	0.84	0.683	0.8	0.776	0.494	0.8
	TNR	0.999	0.999	1	0.999	0.999	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.535	3.517	4.131	3.434	3.672	3.798	3.515	3.688	4.332
	ALL	3.19	3.172	3.213	3.077	3.253	3.017	3.191	3.145	4.186
Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.872	0.818	0.862	0.852	0.706	0.839	0.81	0.522	0.809
	TNR	0.999	0.999	0.892	0.999	0.999	0.938	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.516	3.617		3.514	3.701	3.078	3.597	3.734	3.671
	ALL	3.21	3.191	2.57	3.083	3.178	2.98	3.167	3.184	5.024

Scenario 6		LRV								
	$\delta = 0.7$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.873	0.824	0.928	0.861	0.701	0.877	0.764	0.507	0.826
	TNR	0.999	0.999	0.653	0.999	0.999	0.749	0.999	1	0.94
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 19: Scenario 6, $\delta = 0.7$

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 60	TPR	0.739	0.483	0.769	0.694	0.336	0.567	0.424	0.192	0.337
	TNR	0.999	0.999	0.817	0.999	1	0.989	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.622	3.666	3.654	3.644	3.694	3.403	3.709	3.744	3.929
	ALL	3.201	3.131	3.389	3.201	3.185	3.241	3.213	3.13	2.901
Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 70	TPR	0.777	0.525	0.675	0.736	0.375	0.516	0.556	0.217	0.345
	TNR	0.999	1	1	0.999	1	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.59	3.674	3.726	3.628	3.71	4.014	3.656	3.754	3.539
	ALL	3.22	3.228	2.534	3.144	3.17	3.188	3.132	3.139	4.064
Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 80	TPR	0.784	0.564	0.8	0.733	0.411	0.323	0.598	0.246	0.098
	TNR	0.999	1	1	0.999	1	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.677	3.675	3.843	3.648	3.686	4.154	3.672	3.764	3.786
	ALL	3.186	3.188	3.24	3.1	3.174	2.971	3.138	3.159	2.612
Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 90	TPR	0.812	0.605	0.801	0.798	0.437	0.8	0.649	0.25	0.8
	TNR	0.999	0.999	1	0.999	1	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.628	3.608	3.523	3.68	3.679	4.331	3.607	3.738	3.951
	ALL	3.224	3.126	3.211	3.18	3.211	3.797	3.116	3.149	2.599

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 100	TPR	0.828	0.611	0.807	0.777	0.443	0.799	0.646	0.244	0.535
	TNR	0.999	1	1	0.999	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.65	3.69	4.077	3.689	3.675	4.047	3.695	3.787	4.05
	ALL	3.159	3.092	3.346	3.145	3.141	3.481	3.145	3.193	3.937

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 110	TPR	0.833	0.641	0.8	0.824	0.482	0.8	0.69	0.284	0.798
	TNR	0.999	0.999	1	0.999	1	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.573	3.579	4.158	3.577	3.759	4.127	3.568	3.743	4.388
	ALL	3.198	3.194	1.834	3.241	3.208	3.588	3.188	3.135	2.798

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 120	TPR	0.834	0.656	0.8	0.804	0.49	0.8	0.712	0.29	0.79
	TNR	0.999	0.999	1	0.999	1	1	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.587	3.68	3.549	3.643	3.67	3.603	3.545	3.737	3.302
	ALL	3.198	3.16	3.234	3.247	3.172	4.446	3.254	3.131	3.513

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 130	TPR	0.851	0.686	0.84	0.837	0.529	0.819	0.781	0.339	0.772
	TNR	0.999	0.999	0.954	0.999	1	1	0.999	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB	3.696	3.695	3.927	3.56	3.737	3.808	3.634	3.63	3.157
	ALL	3.219	3.139	3.186	3.155	3.158	3.445	3.104	3.124	3.707

Scenario 6		LRV								
	$\delta = 0.9$	2.37			2.7			3.08		
		ASID	LR	GUIDE	ASID	LR	GUIDE	ASID	LR	GUIDE
Number of Patients: 140	TPR	0.846	0.683	0.868	0.829	0.522	0.83	0.717	0.313	0.741
	TNR	0.999	0.999	0.768	0.999	1	0.942	1	1	1
	SFE	0	0	0	0	0	0	0	0	0
	SUB									
	ALL									

Table 20: Scenario 6, $\delta = 0.9$

Biosketch

Florica Constantine was born on May 6, 1994 in Pittsburgh, PA. She did most of her early schooling in Baden, PA, in the northern outskirts of Pittsburgh, before transitioning into the 'College in High School' program at the University of Pittsburgh during her freshman year of high school and enrolled as a full-time student shortly thereafter. She graduated from the University of Pittsburgh in April 2014 with a degree in Mathematics. In the Fall of 2015, Florica joined Johns Hopkins University as a Masters student in the Department of Applied Mathematics and Statistics. Her research, detailed in this thesis, was advised by Dr. Yanxun Xu. She completed her coursework in December 2016 and this thesis in January 2017. Her research interests are in Bayesian statistics and, more broadly, statistics applied to biology, healthcare, and medicine.